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<p>(54) Title: ANTIVIRAL AGENTS</p> <p>(57) Abstract</p> <p>Compound, compositions and methods are provided which are useful in the suppression and treatment of viral infections, particularly those infections due to viruses in the herpes family.</p>		

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ANTIVIRAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuing application of USSN 60/075,224, filed
5 February 19, 1998, the disclosure of which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

The invention described herein was not made with the aid of any federally sponsored grants.

FIELD OF THE INVENTION

10 The present invention relates generally to biaryl compounds and, more particularly, to novel heteroaryl-substituted benzenes and compositions, their preparation and their use as antiviral agents, particularly against herpes simplex virus.

BACKGROUND OF THE INVENTION

Effective treatments for Herpes Simplex Virus (HSV) types 1 and 2 remain the
15 subject of continued research in a number of laboratories. Both HSV type 1 and 2 show a predilection for infection of the eodermal tissues wherein the infections by the virus cause lesions in the skin, oral cavity, vagina, conjunctiva, and the nervous system. Left untreated, HSV infections can lead to blindness, neonatal deaths and encephalitis.

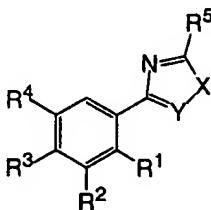
Man serves as the natural host for HSV type 1 and 2 infections whereby the
20 virus is transmitted during close personal contact. Initial or primary infections by HSV types 1 and 2 are contracted through breaks in the mucus membrane. In the healthy carrier the virus can be isolated in the tears, saliva, vaginal and other secretions, even during the absence of overt disease. From the mucus membrane, they are able to replicate and spread to the regional lymph nodes. Occasionally these viruses can infect cells of the haemopoietic system and cause
25 viremia.

One difficulty in treating HSV infections is due to the ability of the viruses to persist in a latent or quiescent form. When the primary infection subsides or recedes, the virus generally resides in a latent form in the sensory nerve ganglia that innervate the site of primary infection. The determinative period of latency of the HSV virus is unknown, but can be
30 affected by heat, cold, sunlight, hormonal and emotional disturbances, or by immunosuppressive agents, resulting generally in recurrent infection.

Treatment of HSV infections has largely been ineffective. A number of strategies to stop the virus have been developed. Generally, the methods involve inhibiting a specific viral function such as adsorption, uncoating, transcription, protein synthesis, nucleic acid acid replication, maturation and release. Acyclovir is currently the preferred medication to
 5 treat HSV1 or HSV2 infections, due to its antiviral effect and low toxicity. However, the emergence of drug-resistant viruses are now limiting the use of this drug.

SUMMARY OF THE INVENTION

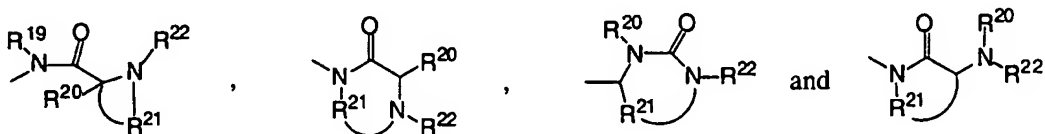
In one aspect, the present invention provides compounds having the formula:



in which the letter X represents S, O or N-R¹⁰, wherein R¹⁰ is hydrogen or lower alkyl, and the
 10 letter Y represents either C-R¹¹ or N, wherein R¹¹ is hydrogen or lower alkyl. In some embodiments, X-Y together represent a divalent radical having the formula -Z¹=Z²-Z³=, wherein Z¹, Z² and Z³ are independently N or C-R¹², in which R¹² is hydrogen or lower alkyl, with the proviso that Z¹, Z² and Z³ are not all N.

The symbol R¹ represents hydrogen or lower alkyl, or when Y is C or contains
 15 a carbon atom at the position adjacent to the bond connecting the two aromatic rings, R¹ can be a linking group between the benzene ring and Y. The linking group will typically be a divalent radical selected from -C(R¹³)(R¹⁴)-, -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-, -C(R¹³)=C(R¹⁵)-, -CH₂O-, -CH₂S-, -CH₂N(R¹⁶)-, -O-, -S-, and -N(R¹⁶)-, wherein R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently hydrogen or lower alkyl.

20 The symbols R², R³ and R⁴ are independently selected from hydrogen, alkyl, heteroalkyl, arylalkyl, arylheteroalkyl, halogen, -CN, -NO₂, alkoxy, arylalkoxy, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), -OR¹⁷, and radicals of the formula:



In the radicals above, R¹⁷ and R¹⁸ are independently selected from hydrogen, alkyl, heteroalkyl, aryl, arylalkyl, and arylheteroalkyl, or, taken together with the nitrogen atom to

which each is attached form a 5-, 6-, or 7-membered ring which is optionally fused with one or two additional aromatic rings. The symbol R^{19} represents hydrogen or lower alkyl, and the symbols R^{20} and R^{22} independently represent hydrogen, lower alkyl, aryl, arylalkyl and arylheteroalkyl. The symbol R^{21} is a divalent radical selected from the group consisting of alkylene and heteroalkylene.

The symbol R^5 represents a hydrogen, lower alkyl, aryl, arylalkyl or $-N(R^{23})(R^{24})$, wherein R^{23} and R^{24} are independently hydrogen, alkyl, heteroalkyl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring.

For those embodiments in which X is S, Y is CH and R^1 , R^2 and R^4 are hydrogen, R^3 is further limited to halogen, -CN, $-NO_2$, $-OR^{17}$ and $-N(R^{17})(R^{18})$, wherein $-N(R^{17})(R^{18})$ is other than $-NH-C(O)-R^{25}$ or $-NH-C(O)-N(R^{26})(R^{27})$ in which R^{25} , R^{26} and R^{27} are independently selected from straight or branched chain alkyl, heteroalkyl, arylalkyl and arylheteroalkyl.

The compounds of the present invention are useful in therapeutic as well as prophylactic and diagnostic applications. Accordingly, the present invention provides compositions containing the above compounds in admixture with pharmaceutically acceptable excipients or diagnostically acceptable excipients. The invention further provides methods of inhibiting or suppressing certain viruses, and methods of treating individuals infected with such viruses, particularly HSV. In addition to treatments for existing conditions, the present invention also provides methods for prophylactic treatments to prevent the onset of viral infection in patients.

Other objects, features and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 provide structures for compounds of formula I in which R^2 and R^3 represent a variety of substituents, including arylalkyl and arylheteroalkyl groups.

Figure 3 provides structures for compounds of formula I in which -X-Y- is varied to provide different amino-substituted heteroaryl groups attached to the benzene ring.

Figure 4 provides structures for compounds of formula I in which R^2 and/or R^3 are electronegative substituents, and -X-Y- is varied to provide different amino-substituted heteroaryl groups attached to the benzene ring.

Figure 5 provides structures for compounds of formula I in which R^3 represents various arylheteroalkyl groups which exhibit conformational restriction due to the presence of an additional ring.

Figure 6 provides structures for compounds of formula I in which R¹ is linked to Y to form fused tricyclic structures.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

5 The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, 10 isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and 15 the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "cycloalkyl" and "alkylene." The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, 20 generally having eight or fewer carbon atoms.

 The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three 25 heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. 30 Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Also included in the term "heteroalkyl" are those radicals described in more detail below as "heteroalkylene" and

“heterocycloalkyl.” The term “heteroalkylene” by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, as well as all other
5 linking groups described herein, no specific orientation of the linking group is implied.

The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include
10 cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms “halo” or “halogen,” by themselves or as part of another substituent,
15 mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “fluoroalkyl,” are meant to include monofluoroalkyl and polyfluoroalkyl.

The term “aryl,” employed alone or in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently.
20 The rings may each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The aryl groups that contain heteroatoms may be referred to as “heteroaryl” and can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-
25 pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl ring
30 systems are selected from the group of acceptable substituents described below.

The terms “arylalkyl” and “arylheteroalkyl” are meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 1-naphthyloxy-3-propyl, and the like). The arylalkyl and arylheteroalkyl groups will typically contain from 1 to 3 aryl
35 moieties attached to the alkyl or heteroalkyl portion by a covalent bond or by fusing the ring to, for example, a cycloalkyl or heterocycloalkyl group. For arylheteroalkyl groups, a heteroatom can occupy the position at which the group is attached to the remainder of the molecule. For example, the term “arylheteroalkyl” is meant to include benzyloxy, 2-phenylethoxy, phenethylamine, and the like.

Each of the above terms (*e.g.*, "alkyl," "heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂ in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted(C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl.

Similarly, substituents for the aryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R' and R'' are independently selected from hydrogen, (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C₁-C₆)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by
5 contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid
10 addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic,
15 isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present
20 invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility
25 in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide a compound of formula I.
30 Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme.

Certain compounds of the present invention can exist in unsolvated forms as well
35 as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions
 5 of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

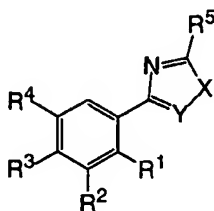
10 General:

The present invention provides compounds, compositions and methods for the inhibition or treatment of viral infections, particularly those due to the herpes family of viruses. Without intending to be bound by a theory, it is believed that the compounds of the present invention exert their effect by interfering with a herpes helicase-primase enzyme, thereby
 15 interfering with the rate-limiting process in herpesvirus DNA replication. In view of the the conservation of herpesvirus helicase-primase across the human herpesviruses, the compounds, compositions and methods of the present invention will be useful in treating (suppressing or inhibiting viral replication) the full spectrum of herpesviruses, including HSV, varicella zoster virus, and cytomegalovirus.

20 Embodiments of the Invention:

Compounds

In one aspect, the present invention provides compounds which are represented by the formula:



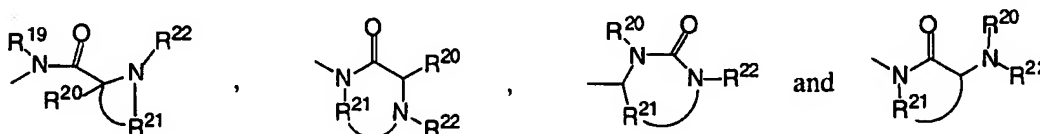
(I).

In formula I, the letter X represents S, O or N-R¹⁰, wherein R¹⁰ is hydrogen or
 25 lower alkyl, and the letter Y represents either N or C-R¹¹, wherein R¹¹ is hydrogen or lower

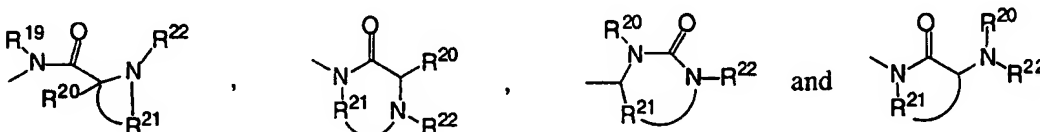
alkyl. Optionally, Y can be linked to R¹ to form an additional ring fused to each of the heterocyclic and benzene ring systems shown in formula I. Still further, X-Y together can be a divalent radical having the formula -Z¹=Z²-Z³=, wherein Z¹, Z² and Z³ are independently N or C(R¹²), in which R¹² is hydrogen or lower alkyl. When X-Y together are a divalent radical, the group will be other than -N=N-N=. In preferred embodiments, X is S, O, NH or N(CH₃). More preferably, X is S. In other preferred embodiments, Y is CH or represents a carbon atom linked to R¹.

The symbol R¹ represents hydrogen or lower alkyl, or when Y is C or contains a carbon atom at the position adjacent to the bond connecting the two aromatic rings, R¹ can be a linking group between the benzene ring and Y. The linking group will typically be a divalent radical selected from -C(R¹³)(R¹⁴)-, -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-, -C(R¹³)=C(R¹⁵)-, -CH₂O-, -CH₂S-, -CH₂N(R¹⁶)-, -O-, -S-, and -N(R¹⁶)-, wherein R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently hydrogen or lower alkyl. Preferably, R¹ is hydrogen or a linking group attached to Y. Preferred linking groups are -C(R¹³)(R¹⁴)- or -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-. More preferably, R¹ is hydrogen or -CH₂CH₂- linked to Y. In the most preferred embodiments, R¹ is hydrogen.

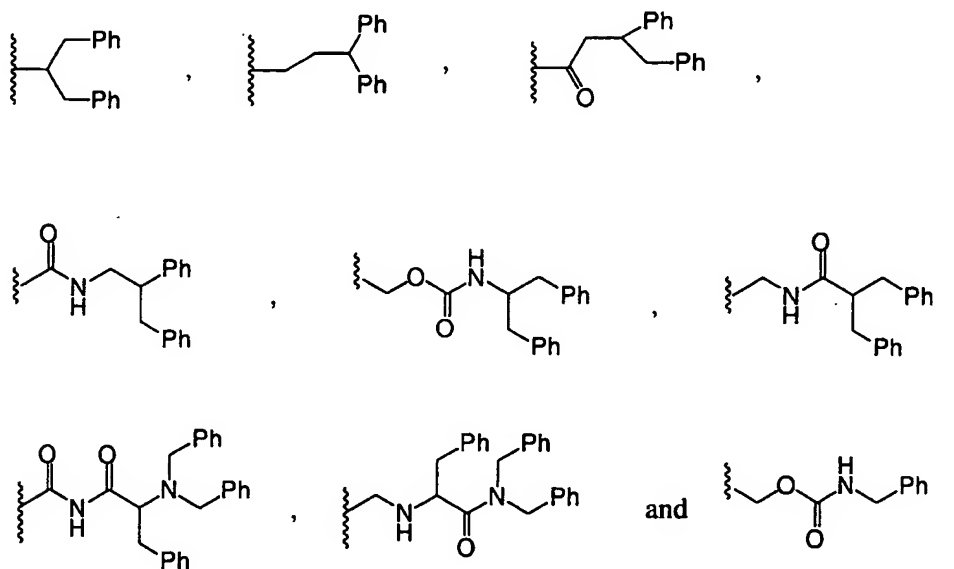
Turning next to the remaining substituents on the benzene ring, the symbols R², R³ and R⁴ independently represent hydrogen, alkyl, heteroalkyl, arylalkyl, arylheteroalkyl, halogen, -CN, -NO₂, alkoxy, arylalkoxy, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), -OR¹⁷, or radicals of the formula:



In the radicals above, R¹⁷ and R¹⁸ independently represent hydrogen, alkyl, heteroalkyl, aryl, arylalkyl or arylheteroalkyl, or, taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring which is optionally fused with one or two additional aromatic rings. The symbol R¹⁹ represents hydrogen or lower alkyl, and the symbols R²⁰ and R²² independently represent hydrogen, lower alkyl, aryl, arylalkyl and arylheteroalkyl. The symbol R²¹ is a divalent radical selected from the group consisting of alkylene and heteroalkylene. In a first group of preferred embodiments, R² is hydrogen and R³ and R⁴ are independently selected from hydrogen, -CF₃, aryl-heteroalkyl, halogen, -NO₂, -N(R¹⁷)(R¹⁸), -SO₂N(R¹⁷)(R¹⁸), and radicals of the formula:



- More preferably, R^2 is hydrogen, one of R^3 or R^4 is selected from the first group of preferred embodiments and the other of R^3 or R^4 is selected from hydrogen, halogen, $-CF_3$ and $-NO_2$. Most preferably, R^2 is hydrogen, one of R^3 or R^4 is selected from hydrogen, $-Br$, $-Cl$, $-CF_3$ and $-NO_2$, and the other of R^3 or R^4 is selected from hydrogen, $-Cl$, $-Br$, $-CF_3$, arylheteroalkyl, $-NH-C(O)-(arylheteroalkyl)$ and $-NO_2$. Exemplary of the arylalkyl and arylheteroalkyl groups in certain preferred embodiments are those having the structures:



- The symbol R^5 represents a hydrogen, lower alkyl, aryl, arylalkyl or $-N(R^{23})(R^{24})$, wherein R^{23} and R^{24} are independently hydrogen, alkyl, heteroalkyl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring. Preferably, R^5 is $-N(R^{23})(R^{24})$, more preferably $-NH_2$, $-NH(CH_3)$ or $-N(CH_3)_2$. In the most preferred embodiments, R^5 is $-NH_2$.

- In addition to the above general description of embodiments and preferred embodiments, additional limitations on the present invention are as follows: when X is S, Y is CH and R^1 , R^2 and R^4 are hydrogen; R^3 will be further limited to halogen, $-CN$, $-NO_2$, $-OR^{17}$ and $-N(R^{17})(R^{18})$, wherein $-N(R^{17})(R^{18})$ is other than $-NH-C(O)-R^{25}$ or $-NH-C(O)-N(R^{26})(R^{27})$ in which R^{25} , R^{26} and R^{27} are independently selected from straight or branched chain alkyl, heteroalkyl, arylalkyl and aryl-heteroalkyl.

- Figures 1-6 provide illustrations of selected compounds of the present invention. In particular, Figure 1 illustrates compounds in which the benzene ring has one or two substituents (other than a 4-(2-aminothiazolyl) group). One of the substituents is a bulky arylalkyl or arylheteroalkyl-containing groups which is attached at either the R^2 or R^3 positions of formula I. In some of the illustrated embodiments, the bulky group is attached to the benzene ring via either a $-NH-$, $-O-$ or $-SO_2NH-$ linkage. A similar group of embodiments is illustrated in Figure 2. In the embodiments of Figure 2, the benzene ring has at least one

electronegative substituent (*e.g.*, -CF₃, -NO₂, -Cl and -Br) and an arylalkyl or arylheteroalkyl-containing substituent (as described for the embodiments illustrated in Figure 1). Figure 3 illustrates exemplary embodiments in which =Y-X- is other than =CH-S-. Illustrated are those compounds in which the 4-(2-aminothiazolyl) group shown in Figures 1 and 2 has been replaced with other heterocycles, for example, oxazolyl, imidazolyl, pyrimidinyl, pyrazinyl, and triazinyl groups. More particularly, compounds are illustrated in which =Y-X- is =CH-O-, =CH-N(CH₃)-, =CH-CH=N-, =CH-N=CH-, =N-CH=CH- and =N-CH=N-. Figure 4 illustrates compounds of the present invention in which R¹ and R⁴ are both hydrogen and R² and R³ are independently hydrogen or an electronegative substituent (*e.g.*, -CF₃, -NO₂, -Cl and -Br), with the proviso that at least one electronegative substituent is present. Figure 5 provides structures for compounds of formula I in which R³ represents various arylheteroalkyl-containing groups. The arylheteroalkyl-containing groups are conformationally restricted due to the presence of an additional ring. Finally, Figure 6 provides structures for compounds of formula I in which R¹ is linked to Y to form fused tricyclic structures.

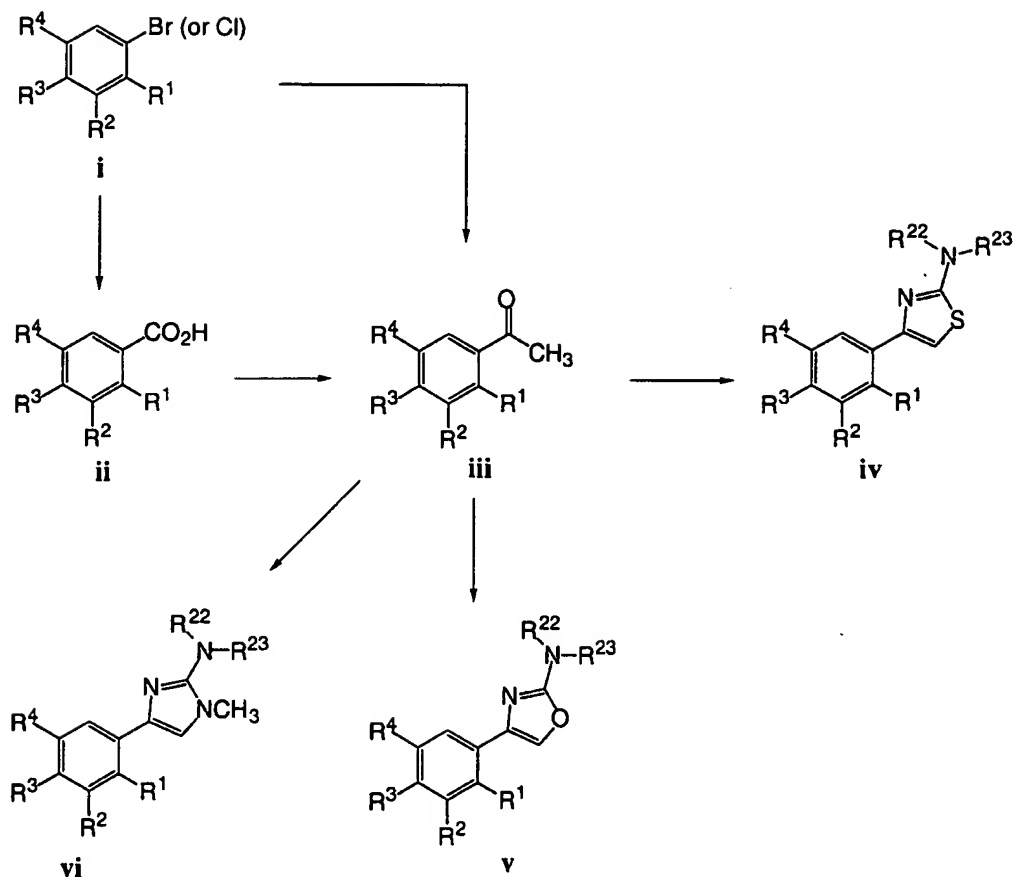
The compounds of the present invention are useful in therapeutic as well as prophylactic and diagnostic applications. Still further, the compounds are useful in the development of additional therapeutic agents as standards in a variety of assay formats. Accordingly, the present invention provides compositions containing the above compounds and pharmaceutically acceptable excipients or diagnostically acceptable excipients. The invention further provides methods of inhibiting or suppressing certain viruses, and methods of treating individuals infected with such viruses, particularly HSV. In addition to treatments for existing conditions, the present invention also provides methods for prophylactic treatments to prevent the onset of viral infection in patient

Preparation of the Compounds

The compounds of the present invention can be prepared as generally described below and depicted in Schemes 1-4. One of skill in the art will appreciate that certain additional steps (*e.g.*, protection and deprotection of certain labile substituents) may be necessary, but are easily accomplished by the skilled artisan.

Scheme 1 provides a general outline for the synthesis of compounds in which X is S, O or N(CH₃) and Y is CH.

SCHEME 1

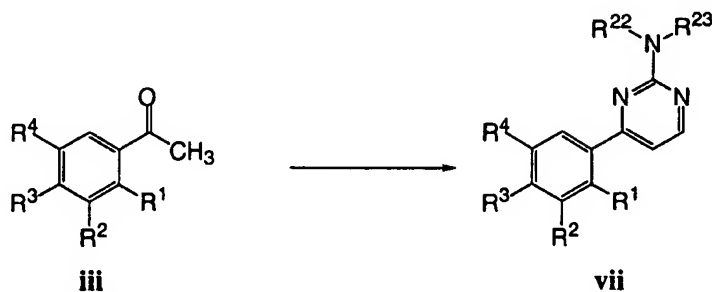


Briefly, a bromo- or chloro-substituted benzene derivative (i, having additional substituents selected from R¹, R², R³ and R⁴) is metallated with either magnesium or ⁿBuLi, and treated with CO₂ (or diethyl carbonate) to form benzoic acid derivative ii, or ethyl acetate (or acetonitrile) to form acetophenone derivative iii. The benzoic acid derivative ii can also be converted to acetophenone iii, upon treatment with methylmagnesium bromide or methyllithium. The acetophenone derivative iii serves as the key intermediate for the preparation of the targets iv, v and vi.

Treatment of iii with bromine and HBr, followed by a substituted thiourea (H₂N-C(S)-N(R²²)(R²³)) provides the target thiazole-substituted benzene derivative iv. Similarly, treatment of iii with bromine and acetic acid, followed by a substituted urea (H₂N-C(O)-N(R²²)(R²³)) provides the target oxazole-substituted benzene derivative v. Still further, bromination of iii can be accomplished using CuBr₂ in chloroform. Treatment of the brominated product with a substituted guanidine (CH₃NH-C(=NH)-N(R²²)(R²³)) provides the target imidazole-substituted benzene derivative vi.

Schemes 2 and 3 illustrate synthesis outlines for the preparation of pyrimidine-substituted benzene derivatives vii and x.

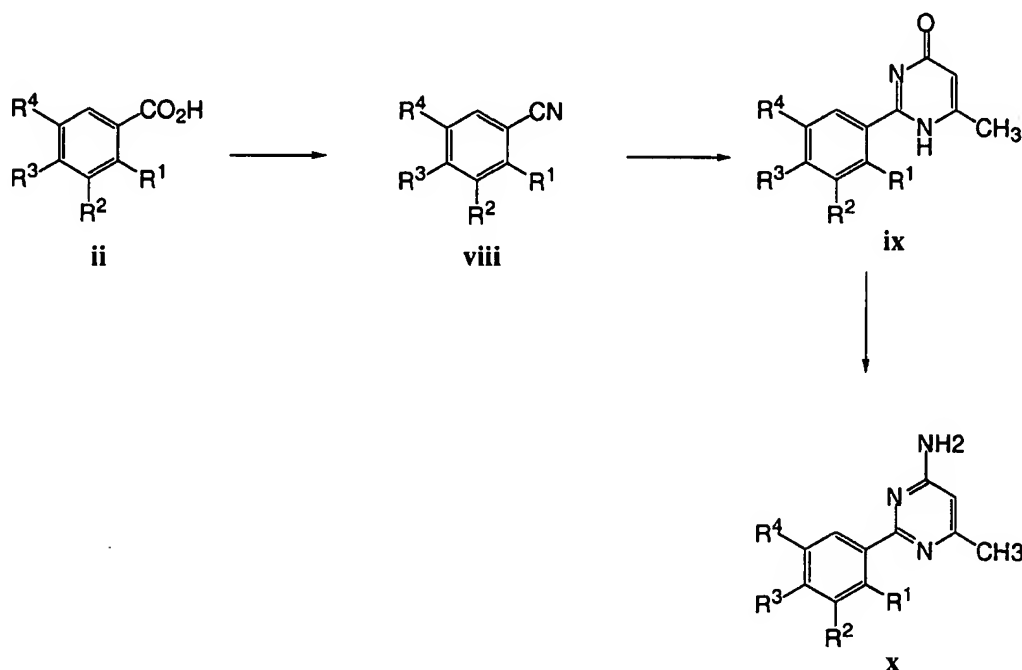
SCHEME 2



As shown in Scheme 2, treatment of **iii** with the formaldehyde equivalent, $\text{HC}(\text{NMe}_2)_3$, in hot toluene, followed by a substituted guanidine ($\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}(\text{R}^{22})(\text{R}^{23})$) provides the target pyrimidinyl-substituted benzene derivative **vii**.

Isomeric pyrimidinyl-substituted benzene derivatives can be obtained starting with benzoic acid **ii** (see Scheme 3).

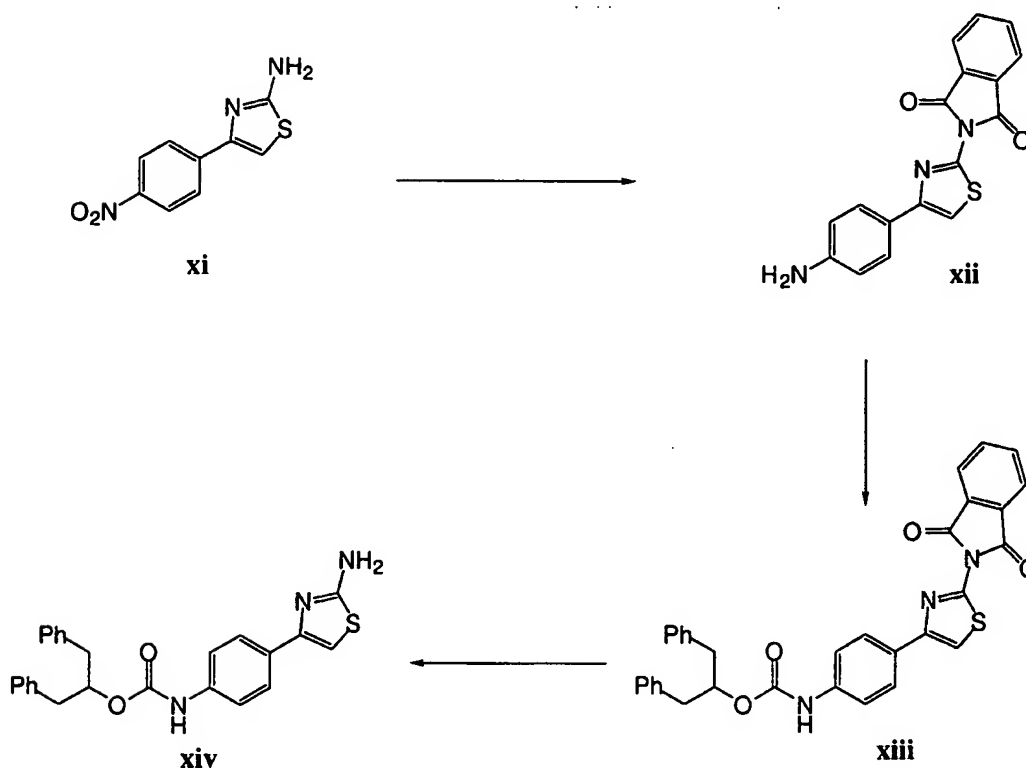
SCHEME 3



Conversion of **ii** to benzonitrile **viii** can be accomplished via Curtius rearrangement, oxidation of the resultant amino group to a diazonium salt (with, for example, HNO_2) and displacement of the diazonium group using CuCN . Alternatively, a number of substituted benzonitriles are commercially available from vendors such as Aldrich Chemical

Co. (Milwaukee, Wisconsin, USA). Treatment of the benzonitrile viii with ammonia in ethanol, followed by ethyl acetoacetate, provides pyrimidone ix. Chlorination of ix can be accomplished with reagents such as POCl₃. Displacement of the chloride can be carried out with a suitable amine, or with ammonium hydroxide, to provide the target pyrimidinyl-substituted benzene compounds x.

SCHEME 4



Scheme 4 illustrates the preparation of compounds of formula I having carbamoyl groups at the R³ position. Briefly, these compounds can be prepared beginning with 2-amino-4-(4-nitrophenyl)thiazole (xi). Conversion of xi to xii can be accomplished by first protecting the 2-amino group (the phthalimido protecting group is illustrated, but other protected groups are useful as well, see for example, Greene and Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, New York, NY (1991)), and then reducing the nitro group to a primary amine using conventional methods (*e.g.*, Fe/HCl). Treatment of xii with a suitable acylating agent (*e.g.*, 1,3-diphenyl-2-propyl chloroformate) provides xiii, which upon removal of the phthalimide protecting group with hydrazine, furnishes target compound xiv.

Analysis of the Compounds

The compounds of the present invention can be evaluated for efficacy against a variety of viruses. In particular, the compounds can be evaluated in a HSV primase gel assay as described in Tenney, *et al*, *J. Biol. Chem.* **270**(16):9129-9136 (1995) or in assays
5 described in commonly owned and co-pending application USSN 08/882,606 (filed June 25, 1997).

Formulation and Administration of the Compounds (Compositions)

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present
10 invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically
15 acceptable carrier or excipient and either a compound of formula I or a pharmaceutically acceptable salt of a compound of formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible
20 granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier
25 having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium
30 carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid
35 dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

5 Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as
10 desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

 Also included are solid form preparations which are intended to be converted,
15 shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

 The pharmaceutical preparation is preferably in unit dosage form. In such form
20 the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

25 The quantity of active component in a unit dose preparation may be varied or adjusted from about 2 mg to about 2000 mg, preferably about 5 mg to about 150 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (*e.g.*, other antiviral agents such as acyclovir, ganciclovir, foscarnet, famciclovir, valaciclovir and cidofovir).

30 In therapeutic use as antiviral agents, the compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.05 mg/kg to about 20 mg/kg daily. A daily dose range of about 0.05 mg/kg to about 2 mg/kg is preferred, with a daily dose range of about 0.05 mg/kg to about 0.2 mg/kg being most preferred. The dosages, however, may be varied depending upon the requirements of the
35 patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until

the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following examples are offered by way of illustration and are not intended to limit the scope of the invention.

5

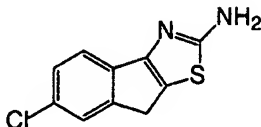
EXAMPLES

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ¹H-NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard 1100 MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1mg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using 1:1 acetonitrile/water with 1% acetic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2mM NH₄OAc in acetonitrile/water as delivery solvent.

20

EXAMPLE 1

This example illustrates the synthesis of 6-chloro-8H-indino[1,2-d]thiazol-2-amine.



The title compound was synthesized from commercially available 5-chloro-1-indanone in two steps.

25

5-Chloro-1-indanone (1 g, 6.0 mmol) was dissolved in benzene (5 mL) and to it was added a solution of bromine (340 μ L, 6.6 mmol) in benzene (10 mL) over a period of 30

min. The reaction was stirred at ambient temperature until the orange color disappeared. The solvent was removed under reduced pressure and the crude product was purified by HPLC chromatography over silica with 30% v/v ethyl acetate/hexane to yield 750 mg of 2-bromo-5-chloro-1-indanone. ¹H-NMR (CDCl₃): δ 7.77 (1H, d, J= 8 Hz), 7.45 (1H, s), 7.40 (1H, d, J= 8 Hz), 4.63 (1H, m), 3.80 (1H, dd), 3.40 (1H, dd).

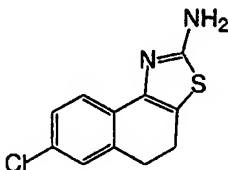
2-Bromo-5-chloro-1-indanone (320 mg, 1.3 mmol) and thiourea (500 mg, 6.6 mmol) were suspended in ethanol (8 mL) and the resulting mixture was heated to reflux. After 30 min of reflux, the reaction was cooled to ambient temperature and was poured into 25 mL of 0.5N NaOH. The crude product precipitated as a white solid. Recrystallization of the crude product from MeOH/H₂O afforded the title compound in 99% yield.

Anal Calcd. for C₁₀H₇ClN₂S: C, 53.94; H, 3.17; Cl, 15.92; N, 12.58; S, 14.40. Found: C, 54.00; H, 3.19; Cl, 15.82; N, 12.52; S, 14.31. Mass spectrum (EI): 222 (M⁺, 100), 187 (M⁺-Cl, 100). ¹H-NMR (CDCl₃): δ 7.44 (1H, d, J= 8 Hz), 7.40 (1H, s), 7.28 (1H, d, J= 8 Hz), 3.67 (1H, s).

15

EXAMPLE 2

This example illustrates the synthesis of 7-chloro-4,5-dihydro-naphthol[1,2-d]thiazol-2-amine.

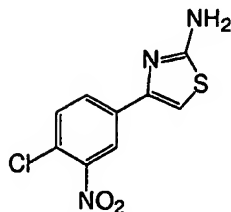


The title compound was prepared from 6-chloro-1-tetralone in a manner similar to that described for 6-chloro-8H-indino[1,2-d]thiazol-2-amine (Example 1). The starting material, 6-chloro-1-tetralone, was prepared according to literature methods (see, Owton and Brunavs, *Synth. Commun.*, **1991**, 21, 981-987). The title compound was obtained as a solid in 99% yield.

Anal Calcd. for C₁₁H₉ClN₂S: C, 55.81; H, 3.83; N, 11.83; S, 13.55. Found: C, 55.88; H, 3.83; N, 11.77; S, 13.59. ¹H-NMR (CDCl₃): δ 7.58 (1H, d, J= 8 Hz), 7.19 (1H, dd, J= 8; 2 Hz), 7.13 (1H, d, J= 2 Hz), 4.98 (2H, bs), 2.98 (2H, t, J= 7 Hz), 2.82 (2H, t, J= 7 Hz).

EXAMPLE 3

This example illustrates the preparation of 2-amino-4-(4-chloro-3-nitrophenyl)thiazole.



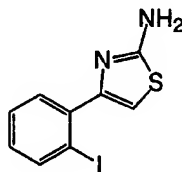
Thiourea (0.100 g, 1.31 mmol) was added to dioxane (7 mL), followed by 3-nitro-4-chlorophenacyl bromide (0.366 g, 1.31 mmol). The solution was stirred at room temperature for eight hours. The title compound was isolated as an oil following silica gel chromatography (CH_2Cl_2 as eluant).

$^1\text{H-NMR}$ (400MHz) (CD_3OD) δ 8.30 (1H, s), 7.94 (1H, m), 7.31 (1H, s).
Mass spectrum (EI): 255 (M^+).

10

EXAMPLE 4

This example illustrates the preparation of 2-amino-4-(2-iodophenyl)thiazole.



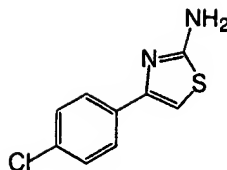
In a similar manner (see Example 3), 2-amino-4-(2-iodophenyl)thiazole was prepared from the corresponding 2-iodophenacyl bromide.

Mass spectrum (EI): 302 (M^+).

15

EXAMPLE 5

This example illustrates the preparation of 2-amino-4-(4-chlorophenyl)thiazole.

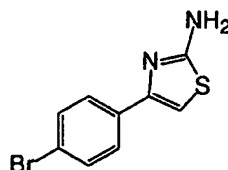


Synthesis was completed as outlined in *J. Org. Chem.*, **1998**, 63, 196-200.

$^1\text{H-NMR}$ (400MHz) (DMSO) δ 7.77 (2H, dd, $J = 2, 7$ Hz), 7.46 (2H, dd, $J = 2, 7$ Hz), 7.15 (1H, s).

EXAMPLE 6

5 This example illustrates the preparation of 2-amino-4-(4-bromophenyl)thiazole.



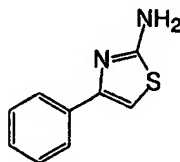
The title compound was prepared using procedures similar to those described for Example 5.

$^1\text{H-NMR}$ (400MHz) (DMSO) δ 7.68 (2H, d, $J = 7$ Hz), 7.62 (2H, d, $J = 7$ Hz), 7.20 (1H, s).

10

EXAMPLE 7

This example illustrates the preparation of 2-amino-4-phenylthiazole.

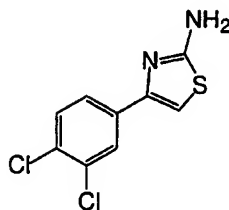


The title compound was prepared using procedures similar to those described for Example 5.

$^1\text{H-NMR}$ (400MHz) (DMSO) δ 7.74 (2H, dd, $J = 2, 7$ Hz), 7.32 - 7.45 (3H, m), 7.12 (1H, s).

EXAMPLE 8

This example illustrates the preparation of 2-amino-4-(3,4-dichlorophenyl)thiazole.

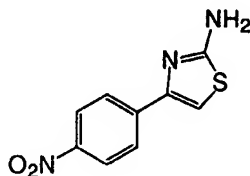


5 The title compound was prepared using procedures similar to those described for Example 5.

$^1\text{H-NMR}$ (400MHz) (DMSO) δ 8.01 (1H, d, $J = 2$ Hz), 7.73 (1H, d, $J = 7$ Hz), 7.65 (1H, d, $J = 7$ Hz), 7.30 (1H, s).

EXAMPLE 9

This example illustrates the preparation of 2-amino-4-(4-nitrophenyl)thiazole.



10 The title compound was prepared using procedures similar to those described for Example 5.

$^1\text{H-NMR}$ (400MHz) (DMSO) δ 8.22 (2H, d, $J = 9$ Hz), 8.02 (2H, d, $J = 9$ Hz), 7.40 (1H, s), 7.24 (2H, s).

EXAMPLE 10

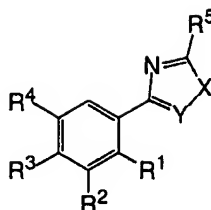
15 This example provides an indication of antiviral activity associated with the compounds described above. The data below was generated using a HSV-1 gel primase assay similar to that described in Tenney, *et al.*, *J. Biol. Chem.* **270**(16):9129-9136 (1995).

<u>Compound (by Example number)</u>	<u>IC₅₀ (μM)</u>
Example 1	100
Example 2	50
Example 3	10
Example 4	.6
Example 5	15
Example 6	30
Example 7	15
Example 8	5
Example 9	5

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein

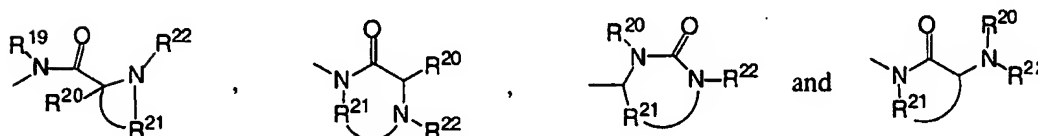
X is selected from the group consisting of S, O and N-R¹⁰, wherein R¹⁰ is hydrogen or lower alkyl;

Y is selected from the group consisting of C-R¹¹ and N, wherein R¹¹ is hydrogen or lower alkyl;

or X-Y together are a divalent radical having the formula -Z¹=Z²-Z³=, wherein Z¹, Z² and Z³ are independently selected from the group consisting of N and C-R¹², wherein R¹² is hydrogen or lower alkyl, with the proviso that Z¹, Z² and Z³ are not all N;

R¹ is a member selected from the group consisting of hydrogen and lower alkyl, or when Y is C or contains a carbon atom at the position adjacent to the bond connecting the two aromatic rings, R¹ is optionally a linking group joining the benzene ring and Y, said linking group being a member selected from the group consisting of -C(R¹³)(R¹⁴)-, -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-, -C(R¹³)=C(R¹⁵)-, -CH₂O-, -CH₂S-, -CH₂N(R¹⁶)-, -O-, -S-, and -N(R¹⁶)-, wherein R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and lower alkyl;

R², R³ and R⁴ are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, arylalkyl, arylheteroalkyl, halogen, -CN, -NO₂, alkoxy, arylalkoxy, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), -OR¹⁷, and radicals of the formula:



wherein

R¹⁷ and R¹⁸ are independently selected from the group consisting of

hydrogen, alkyl, heteroalkyl, aryl, arylalkyl, and arylheteroalkyl, or, taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring which is optionally fused with one or two additional aromatic rings;

R^{19} is selected from the group consisting of hydrogen and lower alkyl;

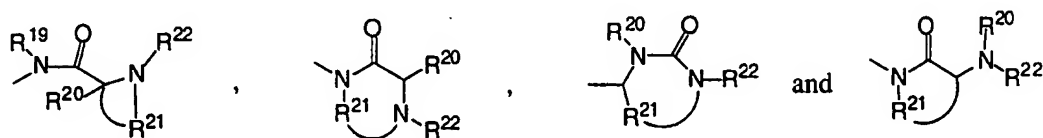
R^{20} and R^{22} are independently selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl and arylheteroalkyl;

R^{21} is a divalent radical selected from the group consisting of alkylene and heteroalkylene; and

R^5 is a member selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl and $-N(R^{23})(R^{24})$, wherein R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring;

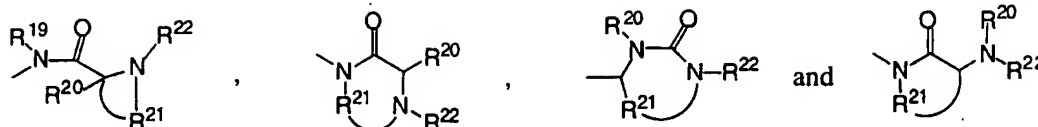
with the proviso that when X is S, Y is CH and R^1 , R^2 and R^4 are hydrogen, R^3 is selected from the group consisting of halogen, $-CN$, $-NO_2$, $-OR^{17}$ and $-N(R^{17})(R^{18})$, wherein $-N(R^{17})(R^{18})$ is other than $-NH-C(O)-R^{25}$ or $-NH-C(O)-N(R^{26})(R^{27})$ in which R^{25} , R^{26} and R^{27} are independently selected from the group consisting of alkyl, heteroalkyl, arylalkyl and arylheteroalkyl.

2. A compound of claim 1, wherein X is selected from the group consisting of S, O, NH and $N(CH_3)$; Y is CH; R^1 and R^2 are both hydrogen; R^3 and R^4 are independently selected from the group consisting of hydrogen, $-CF_3$, aryl-heteroalkyl, halogen, $-NO_2$, $-SO_2N(R^{17})(R^{18})$, $-N(R^{17})(R^{18})$, and radicals of the formula:



and R^5 is $-N(R^{23})(R^{24})$.

3. A compound of claim 1, wherein X is selected from the group consisting of S, O, NH and $N(CH_3)$; R^2 is hydrogen; R^1 represents a linking group to Y, wherein Y is C and said linking group is selected from the group consisting of $-C(R^{13})(R^{14})-$ and $-C(R^{13})(R^{14})-C(R^{15})(R^{16})-$; R^3 and R^4 are independently selected from the group consisting of hydrogen, $-CF_3$, aryl-heteroalkyl, halogen, $-NO_2$, $-SO_2N(R^{17})(R^{18})$, $-N(R^{17})(R^{18})$, and radicals of the formula:



and R^5 is $-N(R^{23})(R^{24})$.

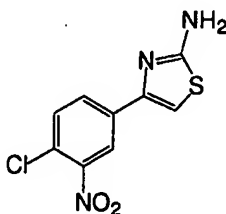
4. A compound of claim 2, wherein X is S; one of R^3 and R^4 is selected from the group consisting of hydrogen, halogen, $-CF_3$ and $-NO_2$; and R^5 is selected from the group consisting of $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

5. A compound of claim 3, wherein X is S; said linking group is $-CH_2CH_2-$; one of R^3 and R^4 is selected from the group consisting of hydrogen, halogen, $-CF_3$ and $-NO_2$; and R^5 is selected from the group consisting of $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

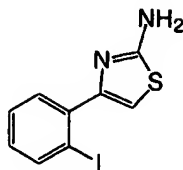
6. A compound of claim 1, wherein X is S, Y is CH; R^1 and R^2 are each hydrogen; and R^3 and R^4 are independently selected from the group consisting of hydrogen, $-CF_3$, $-Cl$, $-Br$, $-NO_2$, aryl-heteroalkyl, $-NH-C(O)-(aryl-heteroalkyl)$ and $-NH-C(O)-NH-R^{27}$.

7. A compound of claim 1, wherein X is S, Y is CH; R^1 and R^2 are each hydrogen; R^3 and R^4 are independently selected from the group consisting of hydrogen, $-CF_3$, $-Cl$, $-Br$, $-NO_2$, aryl-heteroalkyl, $-NH-C(O)-(aryl-heteroalkyl)$ and $-NH-C(O)-NH-R^{27}$; and R^5 is selected from the group consisting of $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

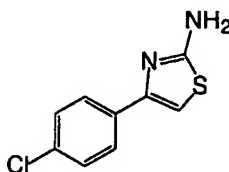
8. A compound of claim 1, having the formula:



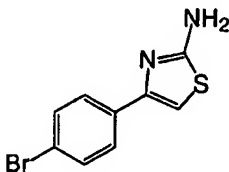
9. A compound of claim 1, having the formula:



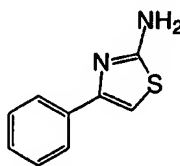
10. A compound of claim 1, having the formula:



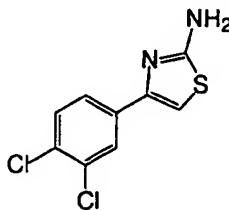
11. A compound of claim 1, having the formula:



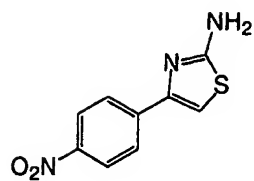
12. A compound of claim 1, having the formula:



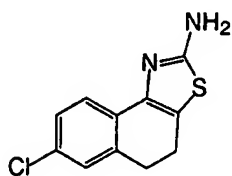
13. A compound of claim 1, having the formula:



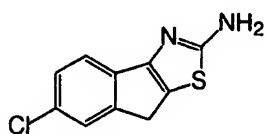
14. A compound of claim 1, having the formula:



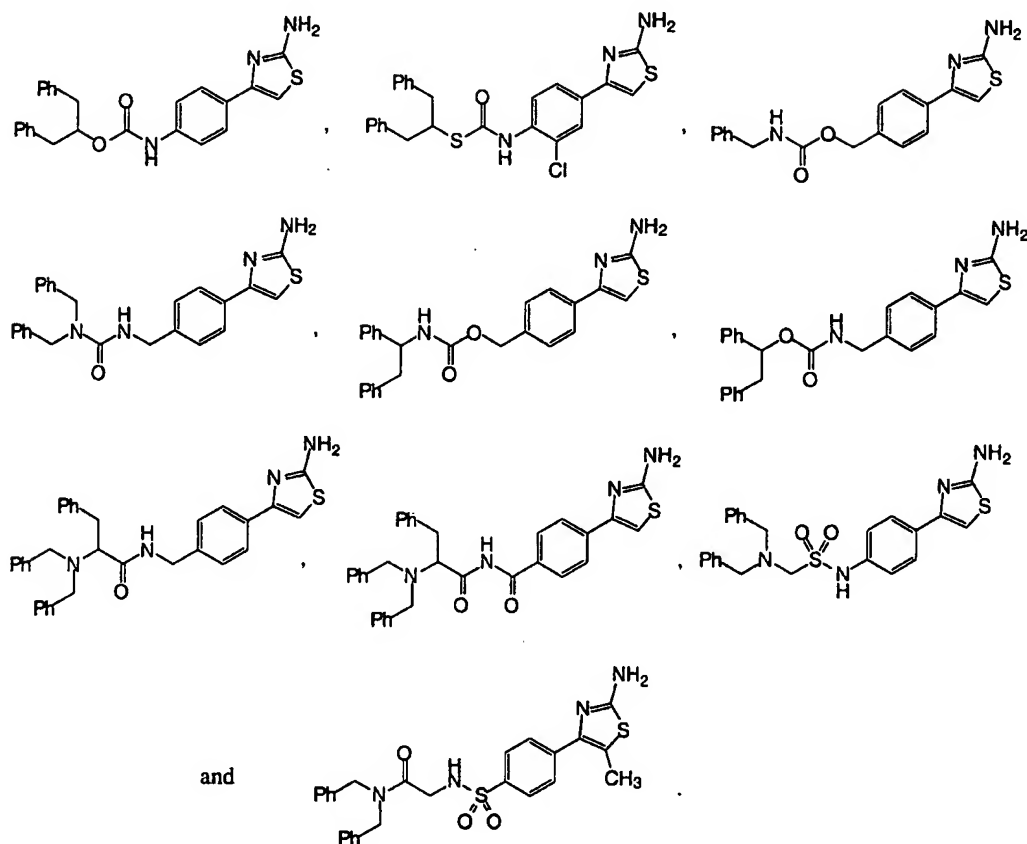
15. A compound of claim 1, having the formula:



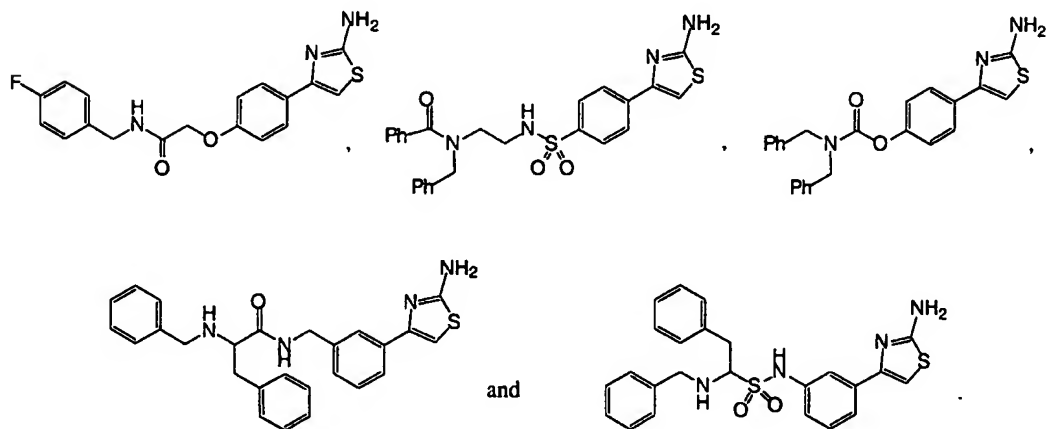
16. A compound of claim 1, having the formula:



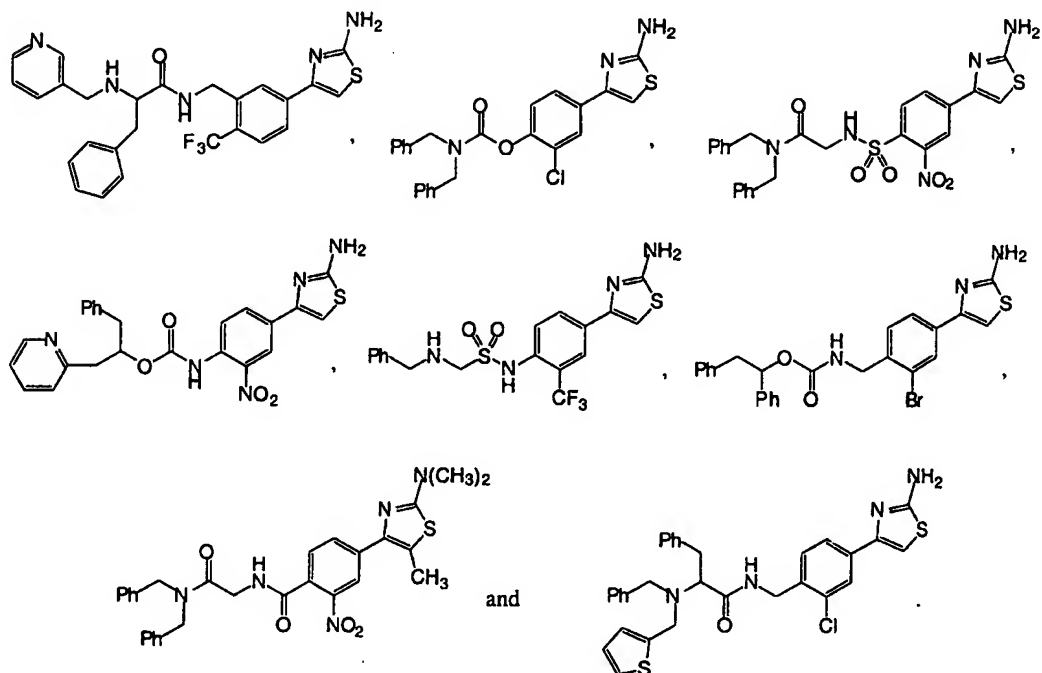
17. A compound of claim 1, selected from the group consisting of:



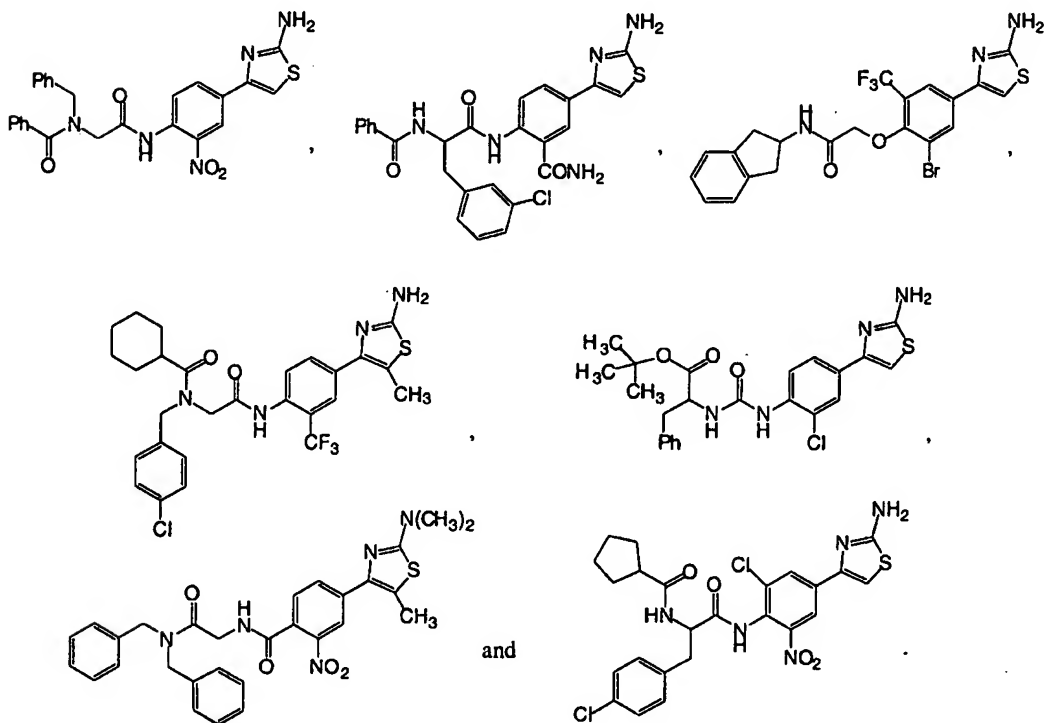
18. A compound of claim 1, selected from the group consisting of:



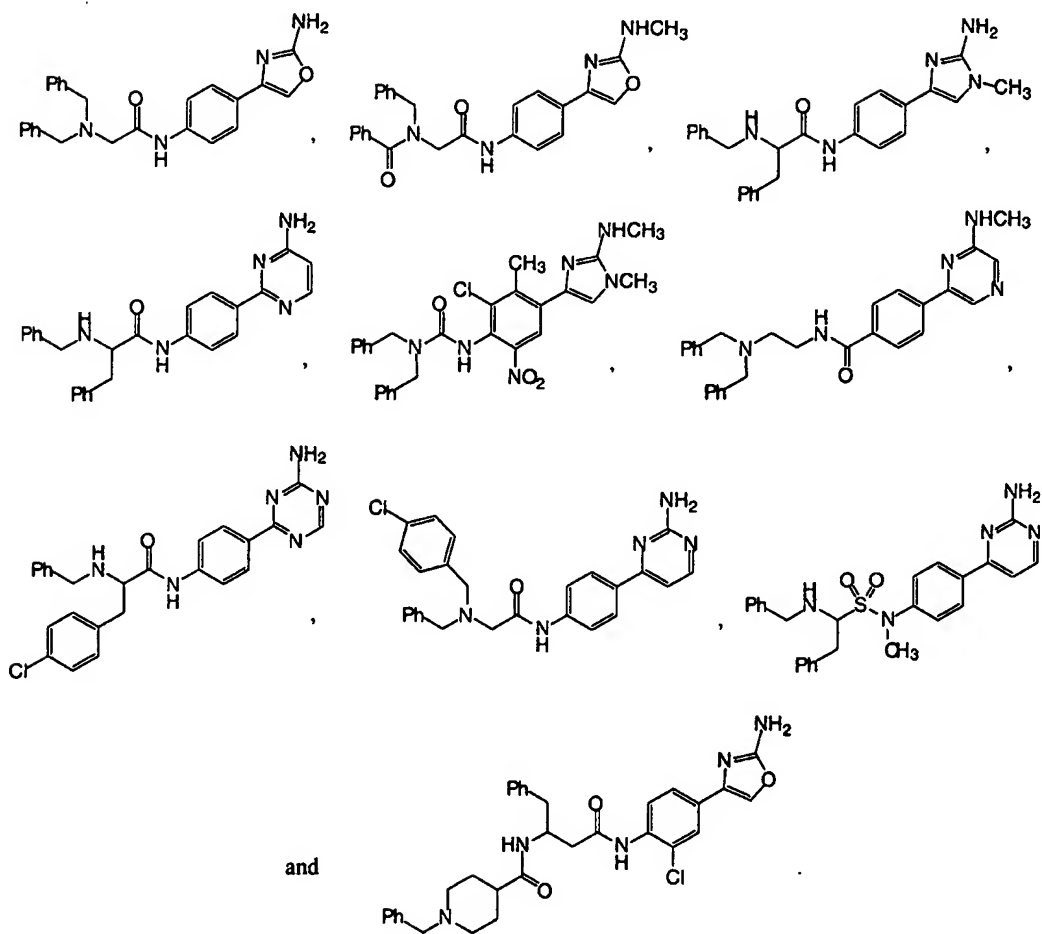
19. A compound of claim 1, selected from the group consisting of:



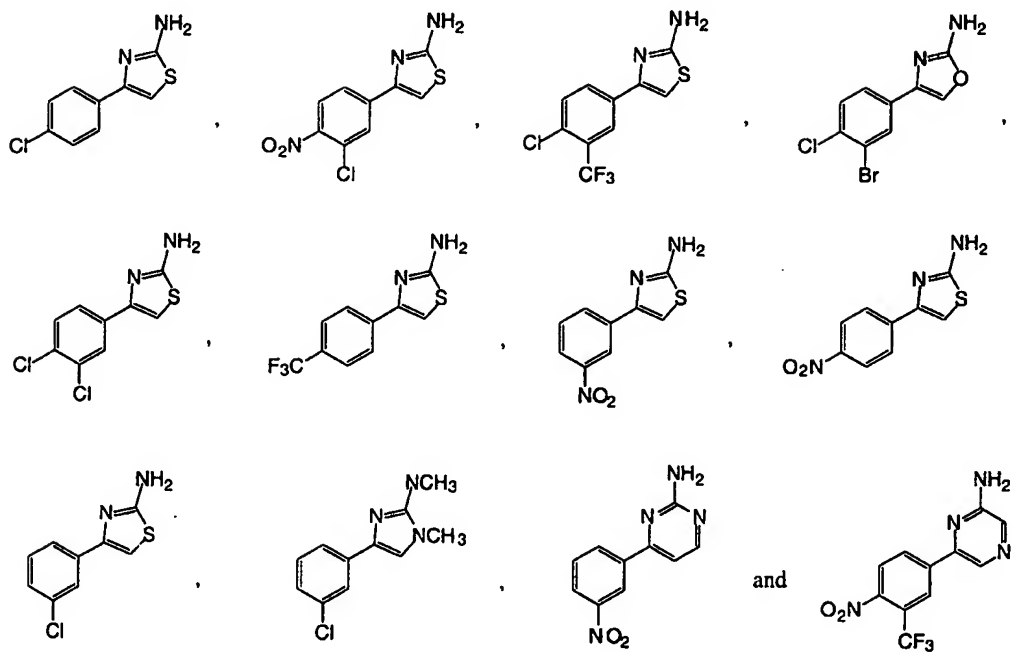
20. A compound of claim 1, selected from the group consisting of:



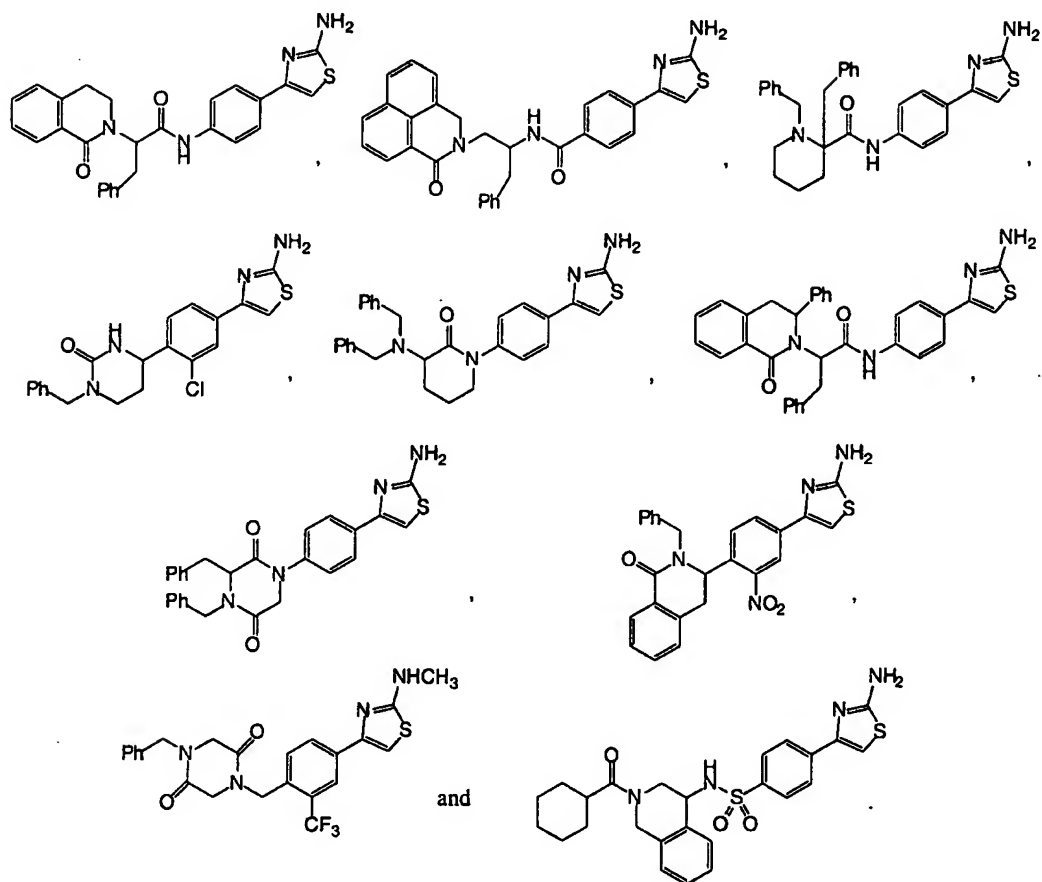
21. A compound of claim 1, selected from the group consisting of:



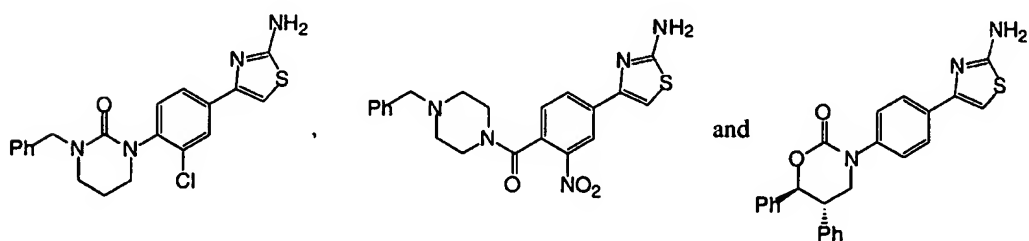
22. A compound of claim 1, selected from the group consisting of:



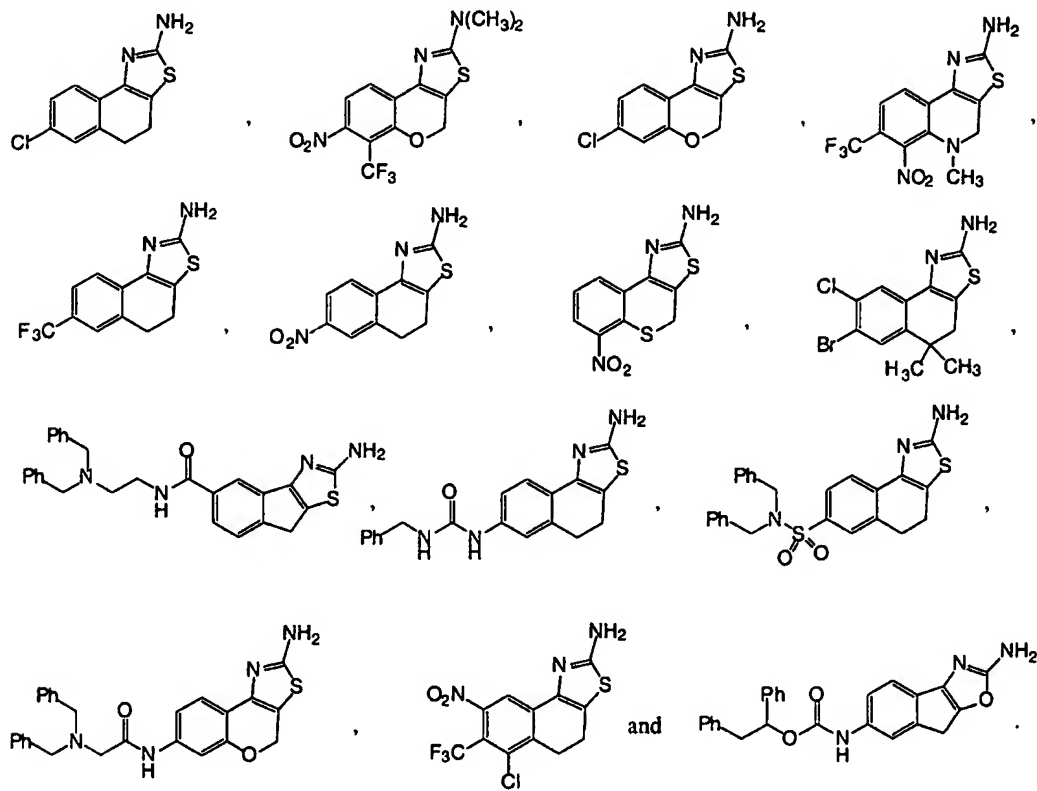
23. A compound of claim 1, selected from the group consisting of:



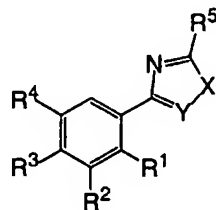
24. A compound of claim 1, selected from the group consisting of:



25. A compound of claim 1, selected from the group consisting of:



26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in admixture with a compound having the formula:



wherein

X is selected from the group consisting of S, O and N-R¹⁰, wherein R¹⁰ is hydrogen or lower alkyl;

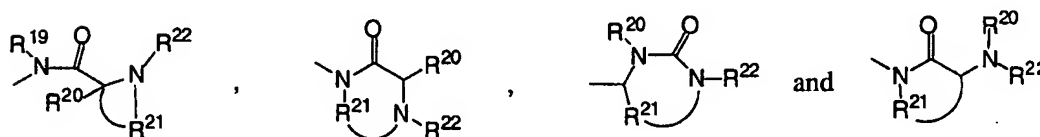
Y is selected from the group consisting of C-R¹¹ and N, wherein R¹¹ is hydrogen or lower alkyl;

or X-Y together are a divalent radical having the formula $-Z^1=Z^2-Z^3=$,

wherein Z^1 , Z^2 and Z^3 are independently selected from the group consisting of N and C- R^{12} , wherein R^{12} is hydrogen or lower alkyl, with the proviso that Z^1 , Z^2 and Z^3 are not all N;

R^1 is a member selected from the group consisting of hydrogen and lower alkyl, or when Y is C or contains a carbon atom at the position adjacent to the bond connecting the two aromatic rings, R^1 is optionally a linking group joining the benzene ring and Y, said linking group being a member selected from the group consisting of -C(R^{13})(R^{14})-, -C(R^{13})(R^{14})-C(R^{15})(R^{16})-, -C(R^{13})=C(R^{15})-, -CH₂O-, -CH₂S-, -CH₂N(R^{16})-, -O-, -S-, and -N(R^{16})-, wherein R^{13} , R^{14} , R^{15} and R^{16} are independently selected from the group consisting of hydrogen and lower alkyl;

R^2 , R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, arylalkyl, arylheteroalkyl, halogen, -CN, -NO₂, alkoxy, arylalkoxy, -SO₂N(R^{17})(R^{18}), -N(R^{17})(R^{18}), -OR¹⁷, and radicals of the formula:



wherein

R^{17} and R^{18} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl, arylalkyl, and arylheteroalkyl, or, taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring which is optionally fused with one or two additional aromatic rings;

R^{19} is selected from the group consisting of hydrogen and lower alkyl;

R^{20} and R^{22} are independently selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl and arylheteroalkyl;

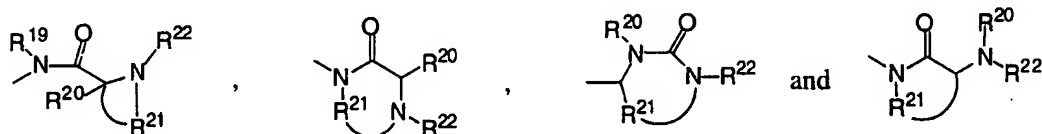
R^{21} is a divalent radical selected from the group consisting of alkylene and heteroalkylene; and

R^5 is a member selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl and -N(R^{23})(R^{24}), wherein R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring;

with the proviso that when X is S, Y is CH and R^1 , R^2 and R^4 are hydrogen, R^3 is selected from the group consisting of halogen, -CN, -NO₂, -OR¹⁷ and -N(R^{17})(R^{18}), wherein -N(R^{17})(R^{18}) is other than -NH-C(O)- R^{25} or -NH-C(O)-N(R^{26})(R^{27}) in which R^{25} , R^{26} and R^{27}

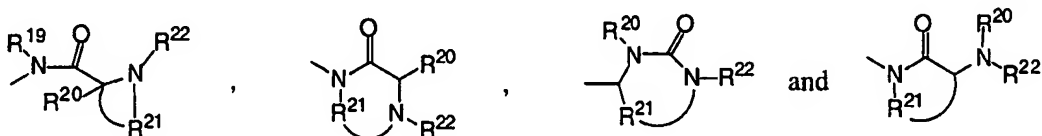
are independently selected from the group consisting of alkyl, heteroalkyl, arylalkyl and arylheteroalkyl.

27. A pharmaceutical composition of claim 26, wherein X is selected from the group consisting of S, O, NH and N(CH₃); Y is CH; R¹ and R² are both hydrogen; R³ and R⁴ are independently selected from the group consisting of hydrogen, -CF₃, aryl-heteroalkyl, halogen, -NO₂, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), and radicals of the formula:



and R⁵ is -N(R²³)(R²⁴).

28. A pharmaceutical composition of claim 26, wherein X is selected from the group consisting of S, O, NH and N(CH₃); R² is hydrogen; R¹ represents a linking group to Y, wherein Y is C and said linking group is selected from the group consisting of -C(R¹³)(R¹⁴)- and -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-; R³ and R⁴ are independently selected from the group consisting of hydrogen, -CF₃, aryl-heteroalkyl, halogen, -NO₂, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), and radicals of the formula:



and R⁵ is -N(R²³)(R²⁴).

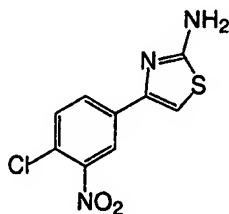
29. A pharmaceutical composition of claim 28, wherein X is S; one of R³ and R⁴ is selected from the group consisting of hydrogen, halogen, -CF₃ and -NO₂; and R⁵ is selected from the group consisting of -NH₂, -NH(CH₃) and -N(CH₃)₂.

30. A pharmaceutical composition of claim 29, wherein X is S; said linking group is -CH₂CH₂-; one of R³ and R⁴ is selected from the group consisting of hydrogen, halogen, -CF₃ and -NO₂; and R⁵ is selected from the group consisting of -NH₂, -NH(CH₃) and -N(CH₃)₂.

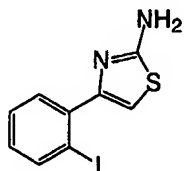
31. A pharmaceutical composition of claim 26, wherein X is S, Y is CH; R¹ and R² are each hydrogen; and R³ and R⁴ are independently selected from the group consisting of hydrogen, -CF₃, -Cl, -Br, -NO₂, aryl-heteroalkyl, -NH-C(O)-(aryl-heteroalkyl) and -NH-C(O)-NH-R²⁷.

32. A pharmaceutical composition of claim 26, wherein X is S, Y is CH; R¹ and R² are each hydrogen; R³ and R⁴ are independently selected from the group consisting of hydrogen, -CF₃, -Cl, -Br, -NO₂, aryl-heteroalkyl, -NH-C(O)-(aryl-heteroalkyl) and -NH-C(O)-NH-R²⁷; and R⁵ is selected from the group consisting of -NH₂, -NH(CH₃) and -N(CH₃)₂.

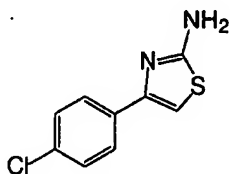
33. A pharmaceutical composition of claim 26, said compound having the formula:



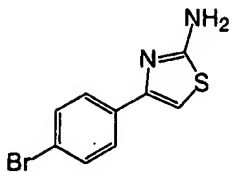
34. A pharmaceutical composition of claim 26, said compound having the formula:



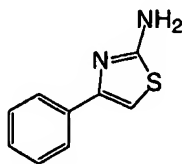
35. A pharmaceutical composition of claim 26, said compound having the formula:



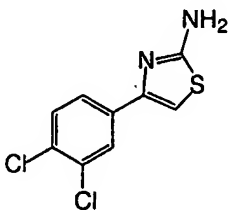
36. A pharmaceutical composition of claim 26, said compound having the formula:



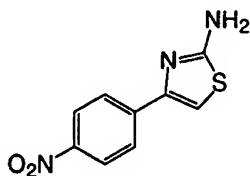
37. A pharmaceutical composition of claim 26, said compound having the formula:



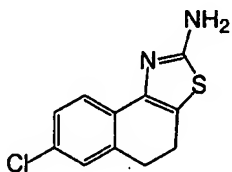
38. A pharmaceutical composition of claim 26, said compound having the formula:



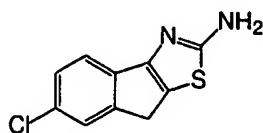
39. A pharmaceutical composition of claim 26, said compound having the formula:



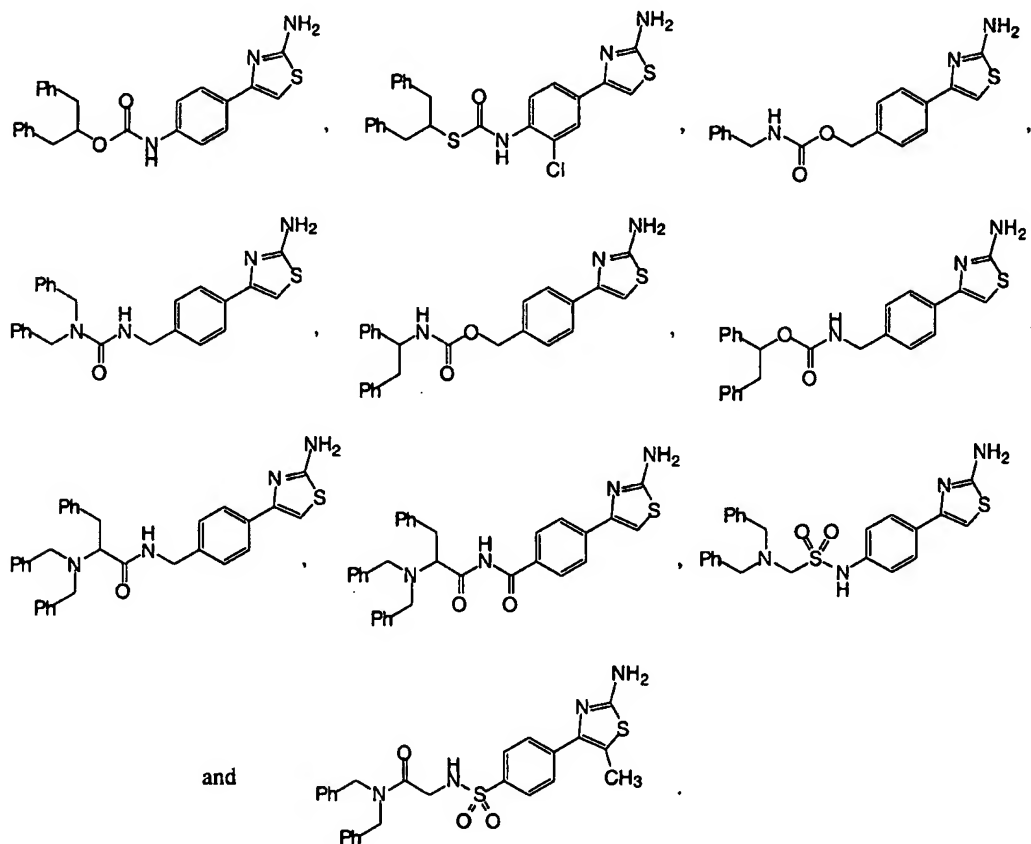
40. A pharmaceutical composition of claim 26, said compound having the formula:



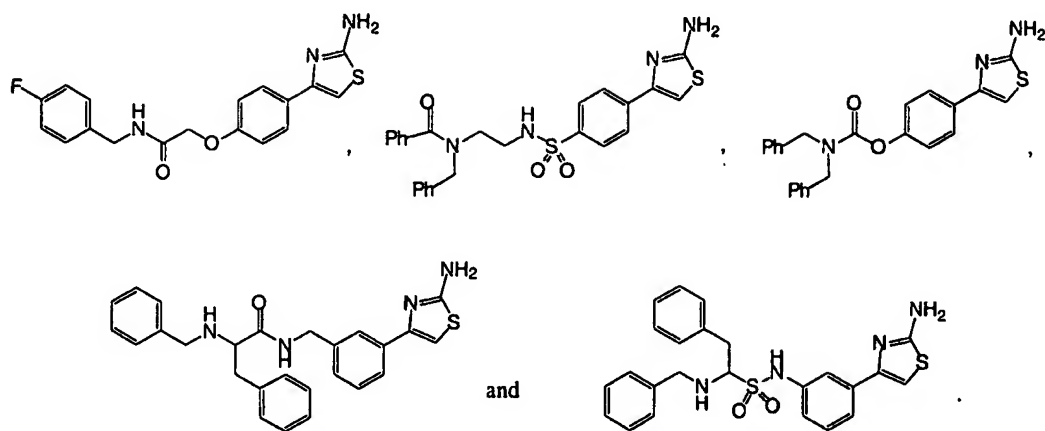
41. A pharmaceutical composition of claim 26, said compound having the formula:



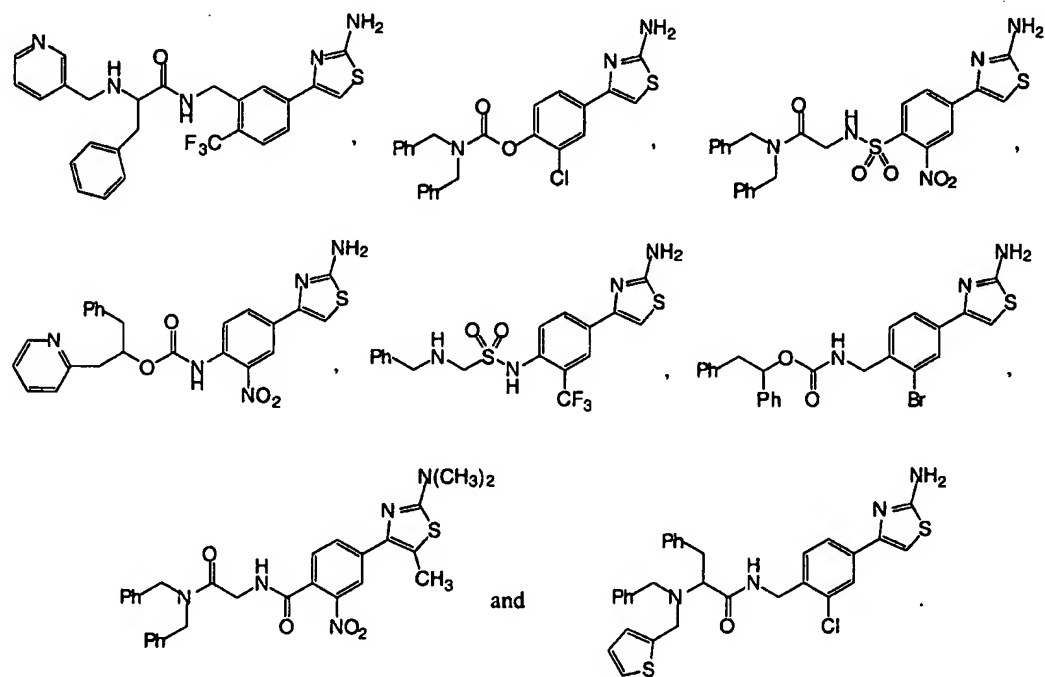
42. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



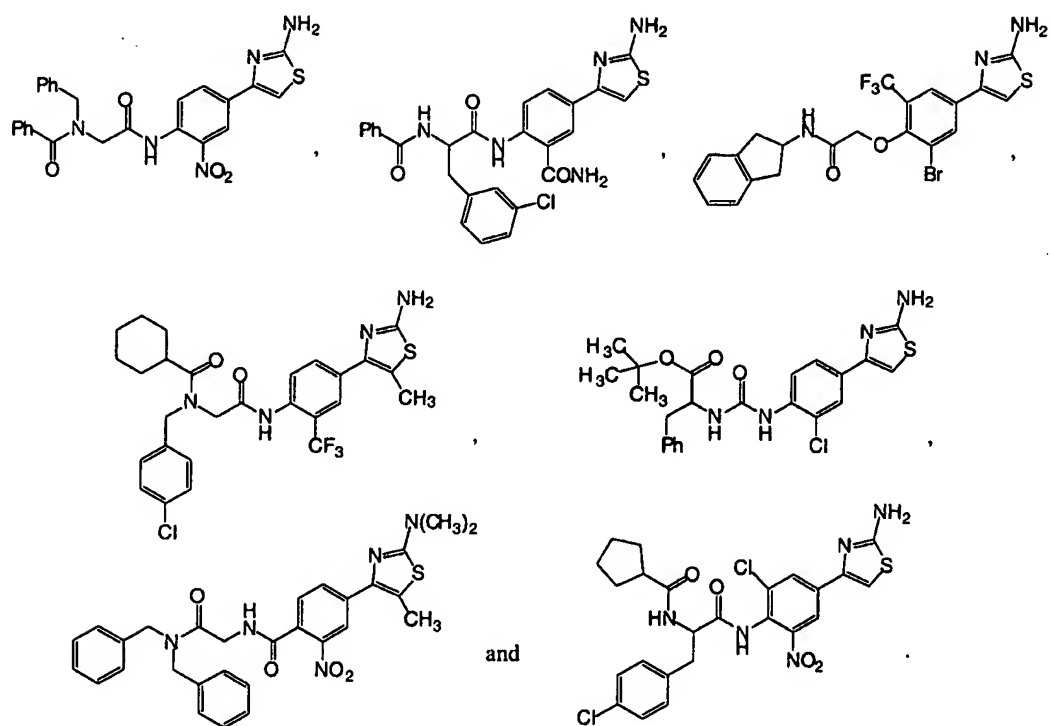
43. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



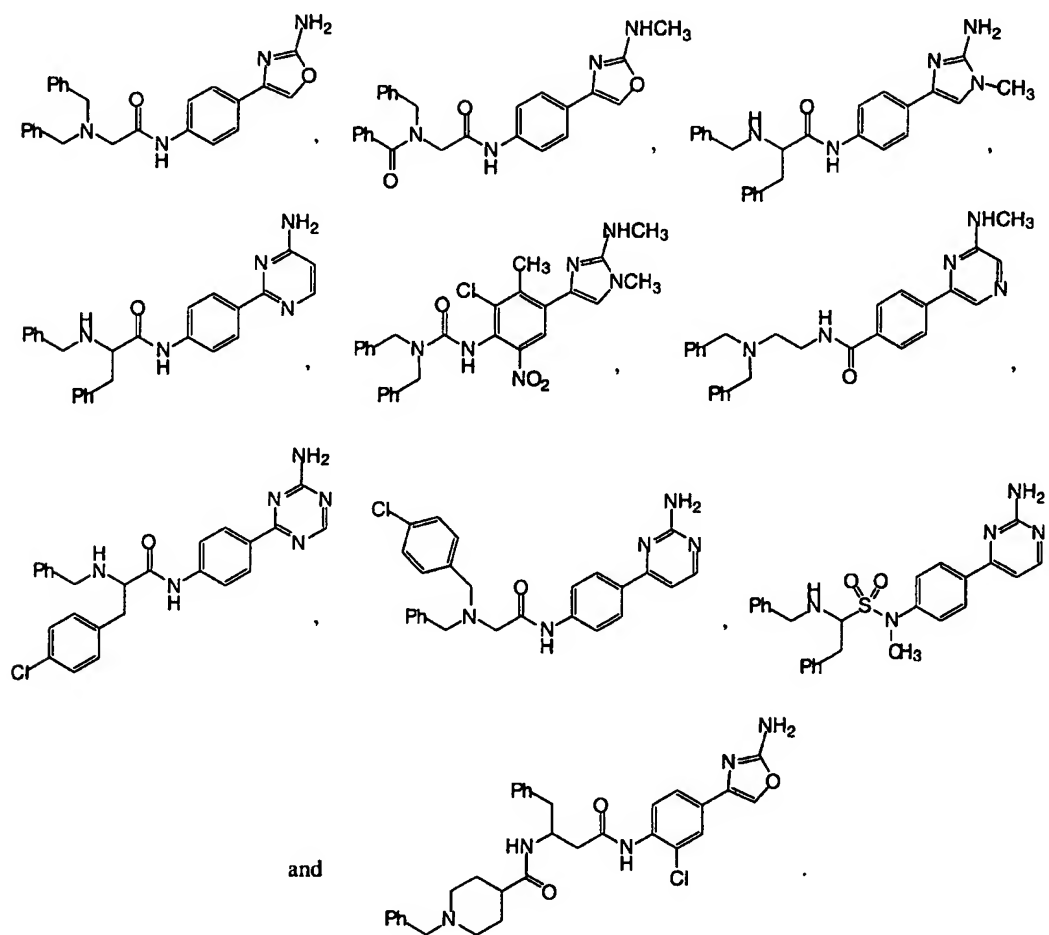
44. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



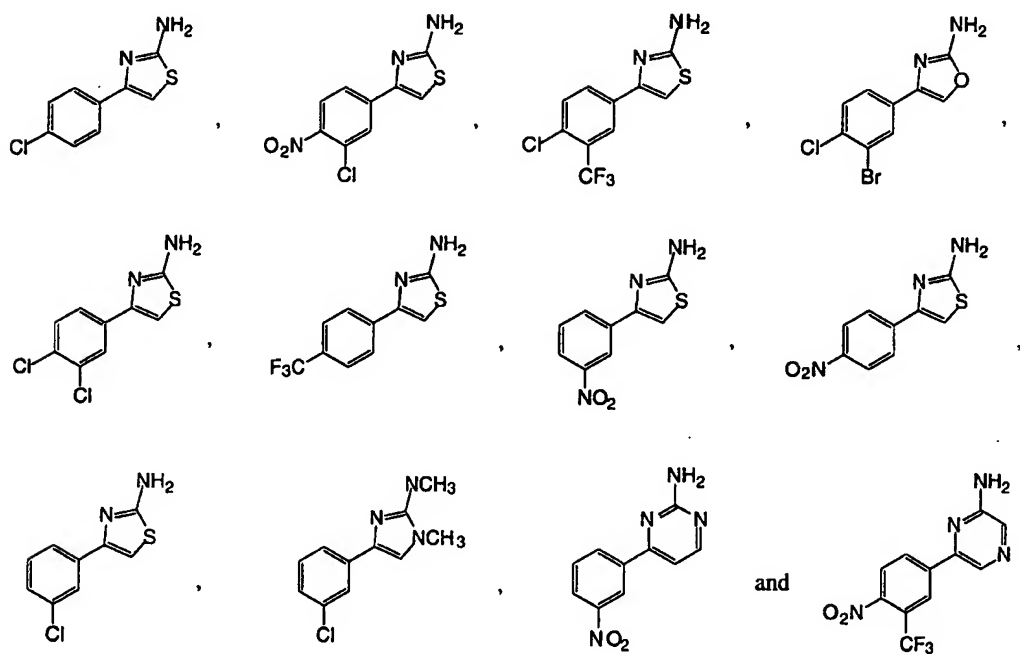
45. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



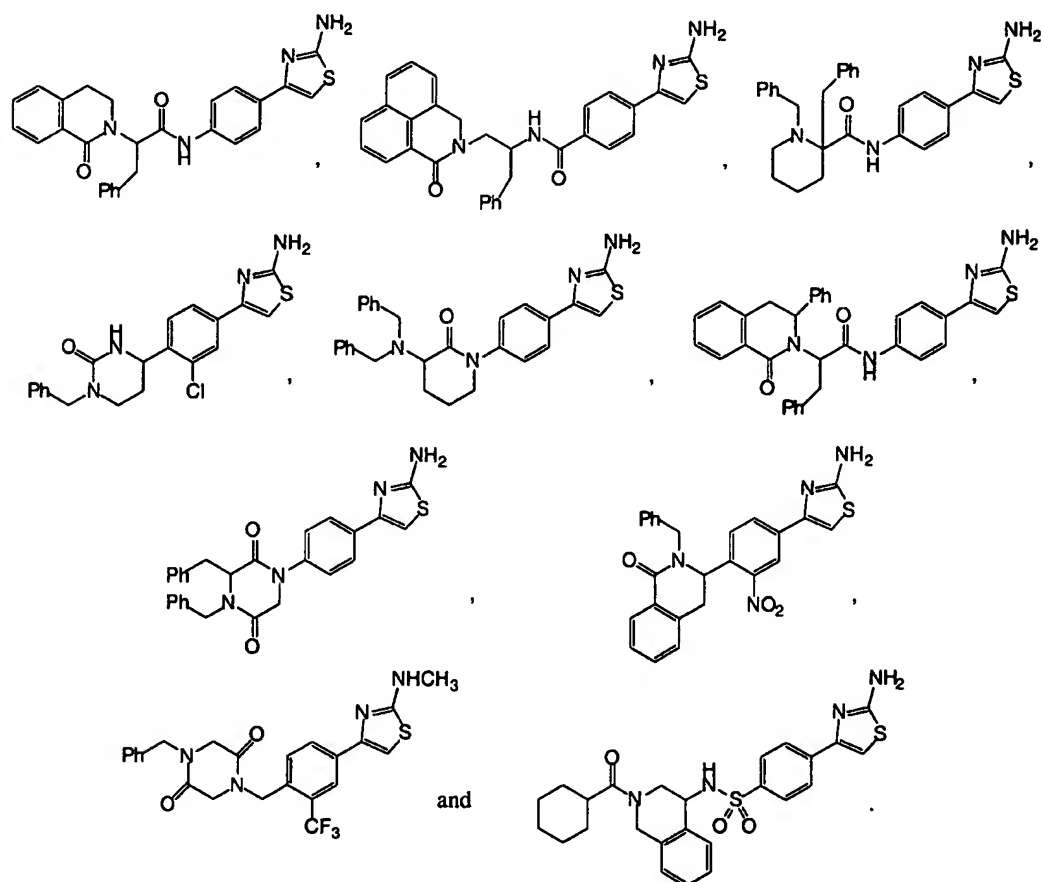
46. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



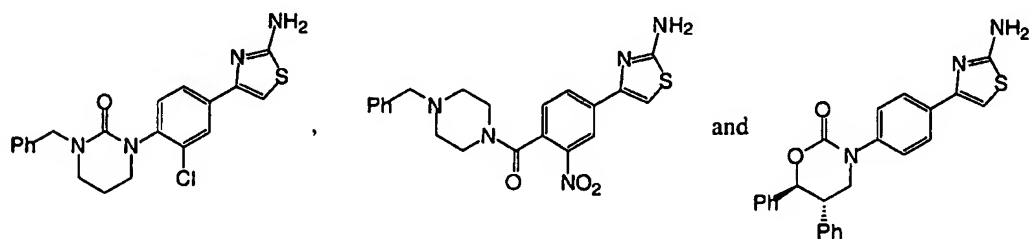
47. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



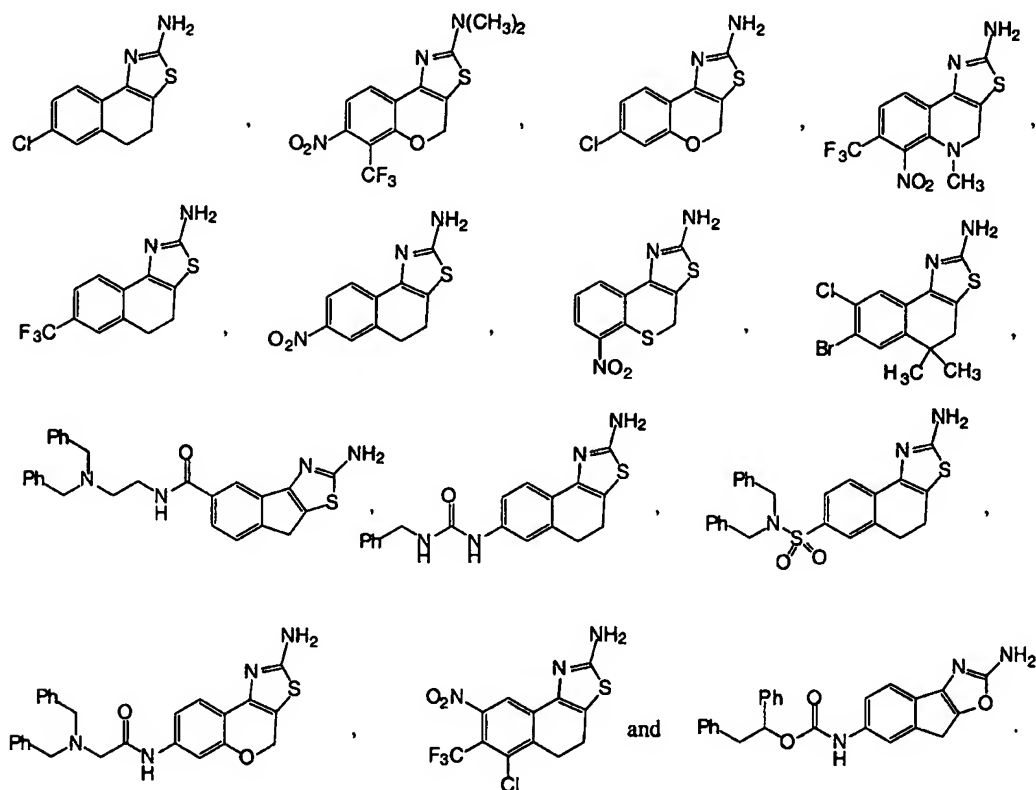
48. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



49. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:

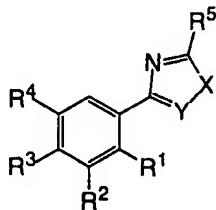


50. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



51. A pharmaceutical composition of claim 26, further comprising an antiviral agent selected from the group consisting of acyclovir, ganciclovir, famciclovir, valaciclovir and foscarnet.

52. A method for preventing or suppressing a viral infection in a mammal, comprising administering to said mammal a viral infection suppressing amount of a compound having the formula:



wherein

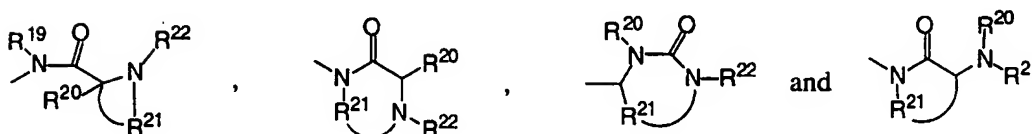
X is selected from the group consisting of S, O and N-R¹⁰, wherein R¹⁰ is hydrogen or lower alkyl;

Y is selected from the group consisting of C-R¹¹ and N, wherein R¹¹ is hydrogen or lower alkyl;

or X-Y together are a divalent radical having the formula -Z¹=Z²-Z³=, wherein Z¹, Z² and Z³ are independently selected from the group consisting of N and C-R¹², wherein R¹² is hydrogen or lower alkyl, with the proviso that Z¹, Z² and Z³ are not all N;

R¹ is a member selected from the group consisting of hydrogen and lower alkyl, or when Y is C or contains a carbon atom at the position adjacent to the bond connecting the two aromatic rings, R¹ is optionally a linking group joining the benzene ring and Y, said linking group being a member selected from the group consisting of -C(R¹³)(R¹⁴)-, -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-, -C(R¹³)=C(R¹⁵)-, -CH₂O-, -CH₂S-, -CH₂N(R¹⁶)-, -O-, -S-, and -N(R¹⁶)-, wherein R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and lower alkyl;

R², R³ and R⁴ are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, arylalkyl, arylheteroalkyl, halogen, -CN, -NO₂, alkoxy, arylalkoxy, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), -OR¹⁷, and radicals of the formula:



wherein

R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl, arylalkyl, and arylheteroalkyl, or, taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring which is optionally fused with one or two additional aromatic rings;

R¹⁹ is selected from the group consisting of hydrogen and lower alkyl;

R²⁰ and R²² are independently selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl and arylheteroalkyl;

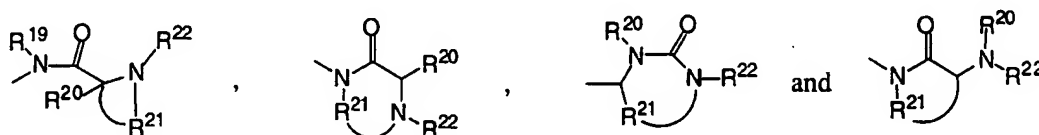
R²¹ is a divalent radical selected from the group consisting of alkylene and heteroalkylene; and

R⁵ is a member selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl and -N(R²³)(R²⁴), wherein R²³ and R²⁴ are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl and arylalkyl, or

taken together with the nitrogen atom to which each is attached form a 5-, 6-, or 7-membered ring;

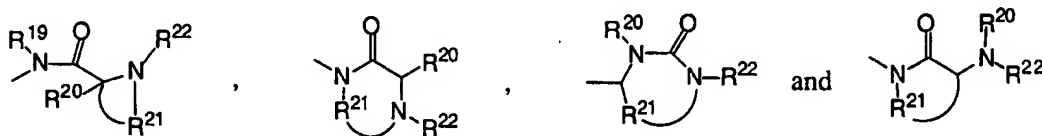
with the proviso that when X is S, Y is CH and R^1 , R^2 and R^4 are hydrogen, R^3 is selected from the group consisting of halogen, -CN, -NO₂, -OR¹⁷ and -N(R¹⁷)(R¹⁸), wherein -N(R¹⁷)(R¹⁸) is other than -NH-C(O)-R²⁵ or -NH-C(O)-N(R²⁶)(R²⁷) in which R²⁵, R²⁶ and R²⁷ are independently selected from the group consisting of alkyl, heteroalkyl, arylalkyl and arylheteroalkyl.

53. A method in accordance with claim 52, wherein X is selected from the group consisting of S, O, NH and N(CH₃); Y is CH; R^1 and R^2 are both hydrogen; R^3 and R^4 are independently selected from the group consisting of hydrogen, -CF₃, aryl-heteroalkyl, halogen, -NO₂, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), and radicals of the formula:



and R⁵ is -N(R²³)(R²⁴).

54. A method in accordance with claim 52, wherein X is selected from the group consisting of S, O, NH and N(CH₃); R^2 is hydrogen; R^1 represents a linking group to Y, wherein Y is C and said linking group is selected from the group consisting of -C(R¹³)(R¹⁴)- and -C(R¹³)(R¹⁴)-C(R¹⁵)(R¹⁶)-; R^3 and R^4 are independently selected from the group consisting of hydrogen, -CF₃, aryl-heteroalkyl, halogen, -NO₂, -SO₂N(R¹⁷)(R¹⁸), -N(R¹⁷)(R¹⁸), and radicals of the formula:



and R⁵ is -N(R²³)(R²⁴).

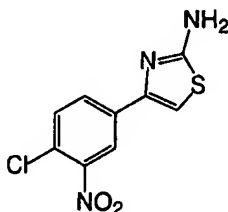
55. A method in accordance with claim 54, wherein X is S; one of R^3 and R^4 is selected from the group consisting of hydrogen, halogen, -CF₃ and -NO₂; and R⁵ is selected from the group consisting of -NH₂, -NH(CH₃) and -N(CH₃)₂.

56. A method in accordance with claim 55, wherein X is S; said linking group is -CH₂CH₂-; one of R^3 and R^4 is selected from the group consisting of hydrogen, halogen, -CF₃ and -NO₂; and R⁵ is selected from the group consisting of -NH₂, -NH(CH₃) and -N(CH₃)₂.

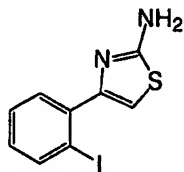
57. A method in accordance with claim 52, wherein X is S, Y is CH; R¹ and R² are each hydrogen; and R³ and R⁴ are independently selected from the group consisting of hydrogen, -CF₃, -Cl, -Br, -NO₂, aryl-heteroalkyl, -NH-C(O)-(aryl-heteroalkyl) and -NH-C(O)-NH-R²⁷.

58. A method in accordance with claim 52, wherein X is S, Y is CH; R¹ and R² are each hydrogen; R³ and R⁴ are independently selected from the group consisting of hydrogen, -CF₃, -Cl, -Br, -NO₂, aryl-heteroalkyl, -NH-C(O)-(aryl-heteroalkyl) and -NH-C(O)-NH-R²⁷; and R⁵ is selected from the group consisting of -NH₂, -NH(CH₃) and -N(CH₃)₂.

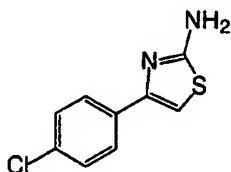
59. A method in accordance with claim 52, said compound having the formula:



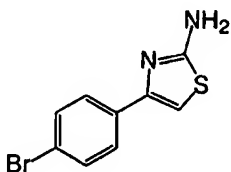
60. A method in accordance with claim 52, said compound having the formula:



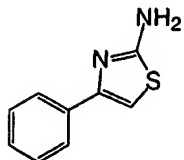
61. A method in accordance with claim 52, said compound having the formula:



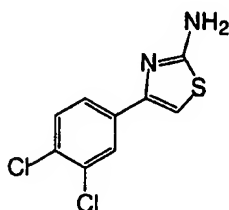
62. A method in accordance with claim 52, said compound having the formula:



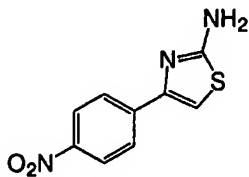
63. A method in accordance with claim 52, said compound having the formula:



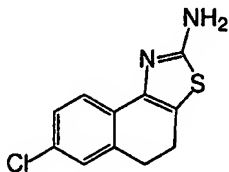
64. A method in accordance with claim 52, said compound having the formula:



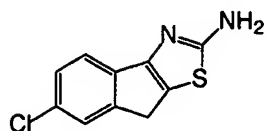
65. A method in accordance with claim 52, said compound having the formula:



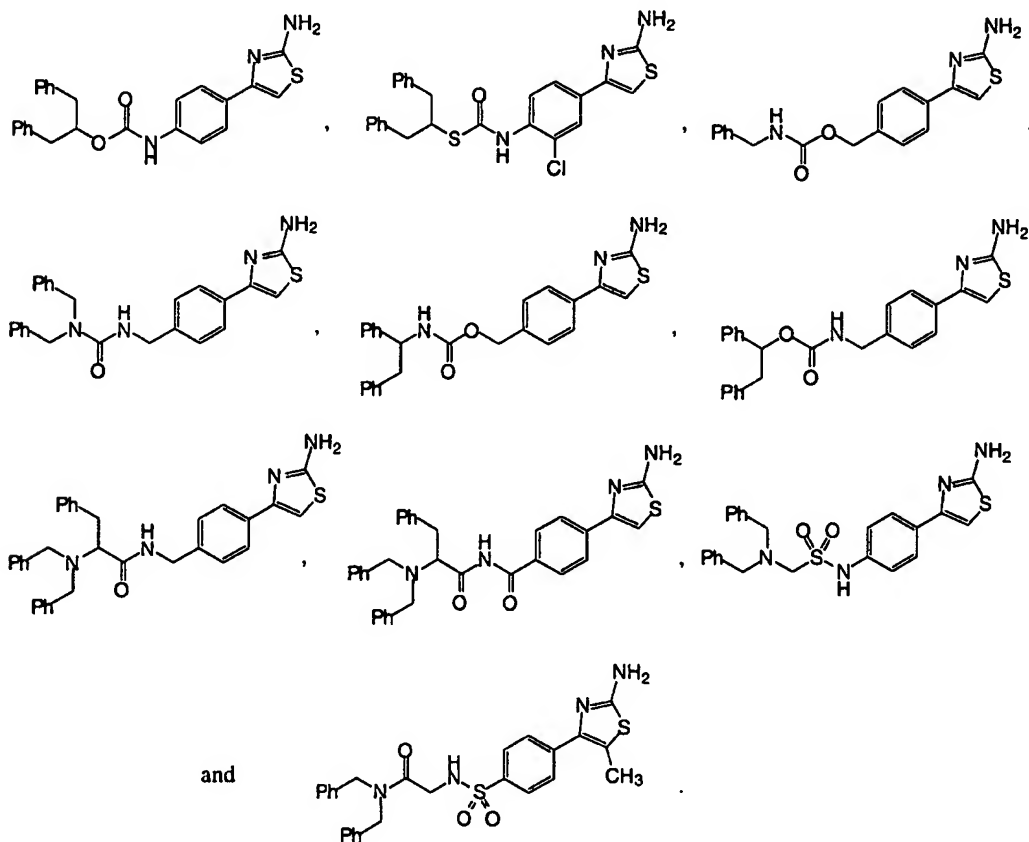
66. A method in accordance with claim 52, said compound having the formula:



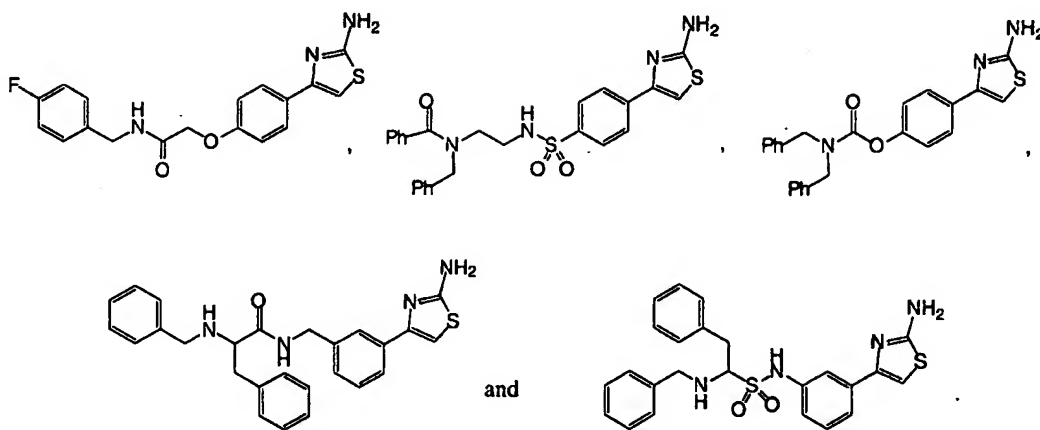
67. A method in accordance with claim 52, said compound having the formula:



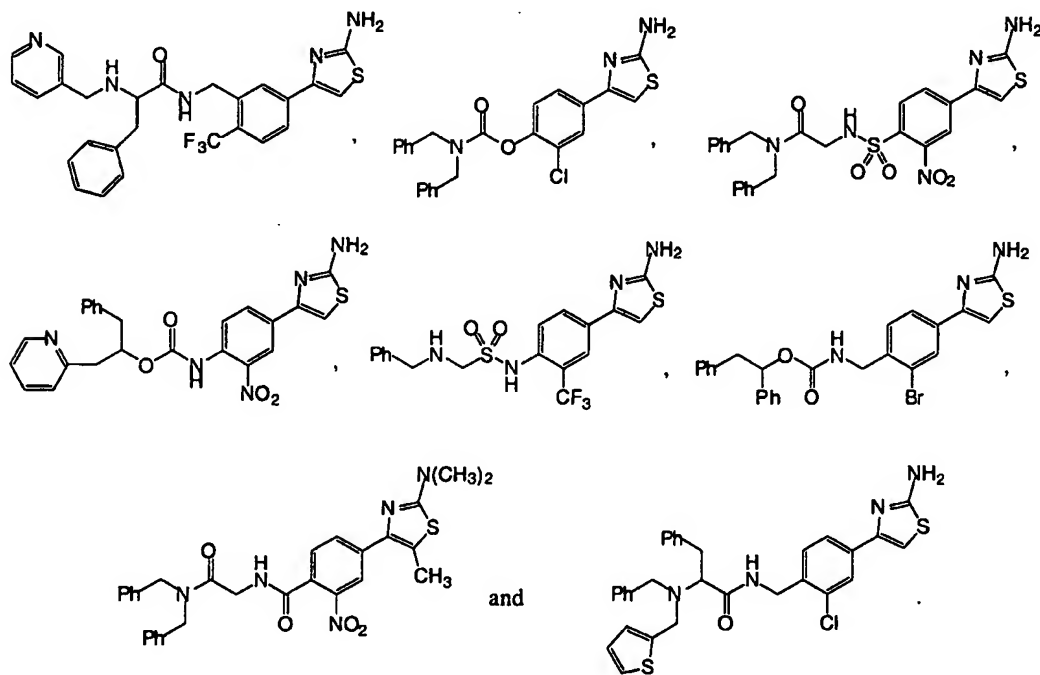
68. A method in accordance with claim 52, said compound selected from the group consisting of:



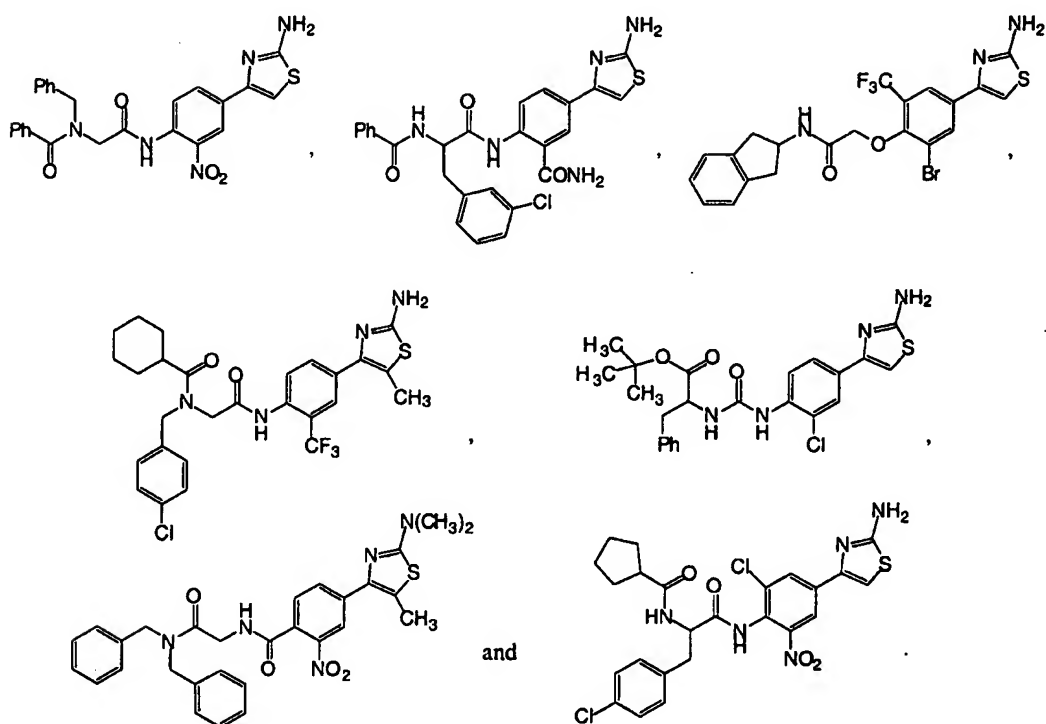
69. A method in accordance with claim 52, said compound selected from the group consisting of:



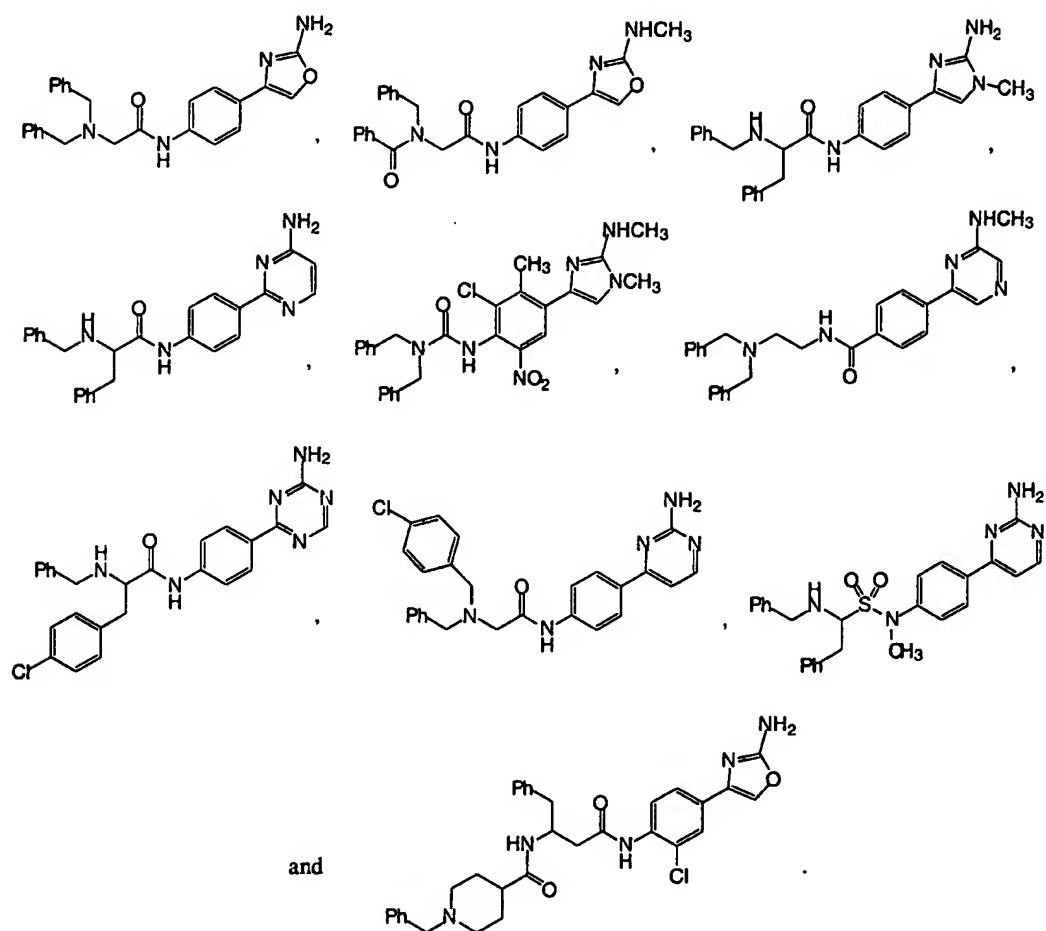
70. A method in accordance with claim 52, said compound selected from the group consisting of:



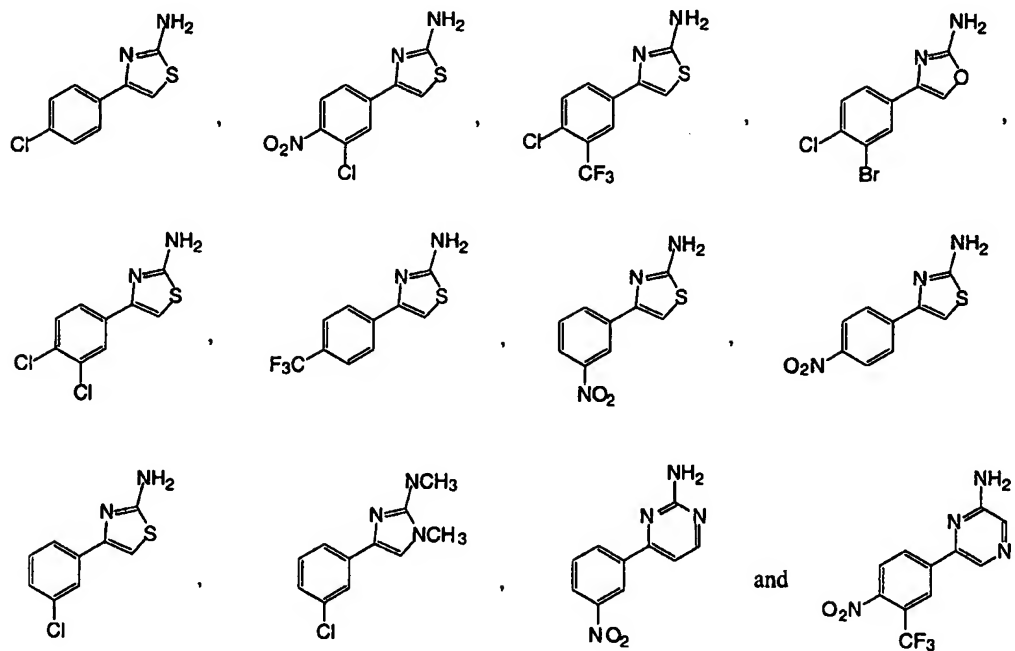
71. A method in accordance with claim 52, said compound selected from the group consisting of:



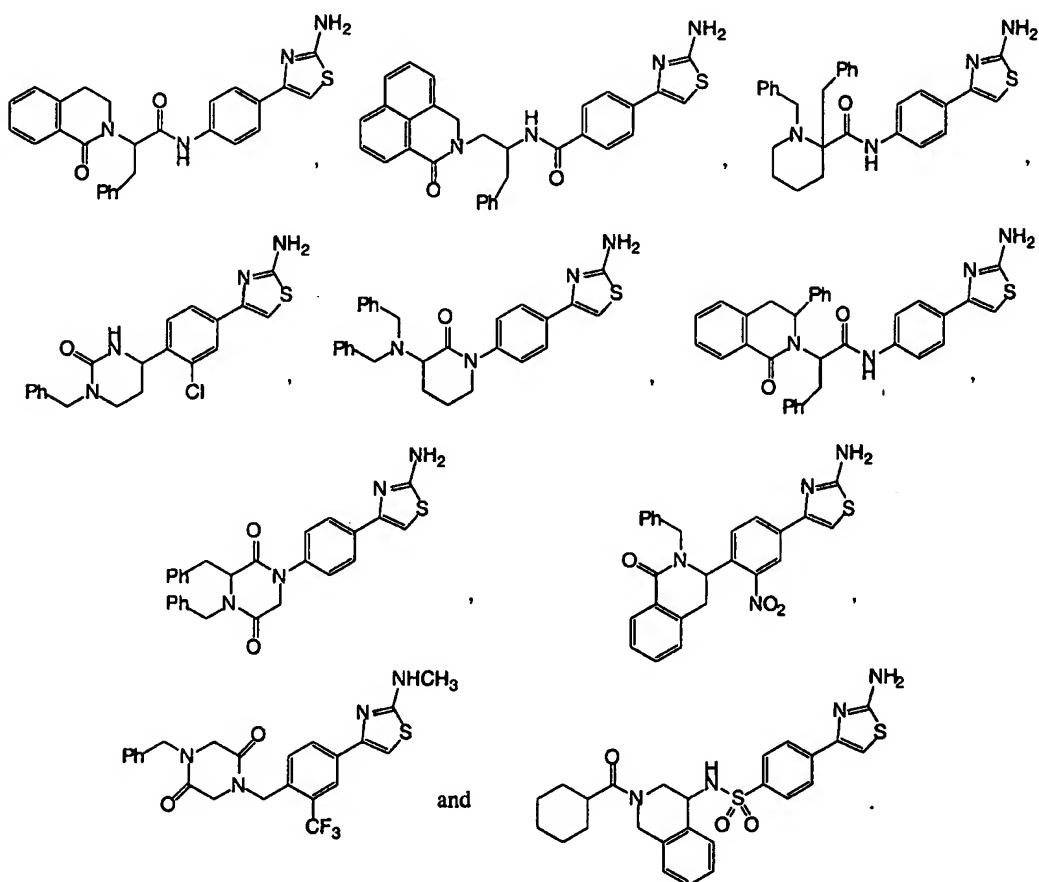
72. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



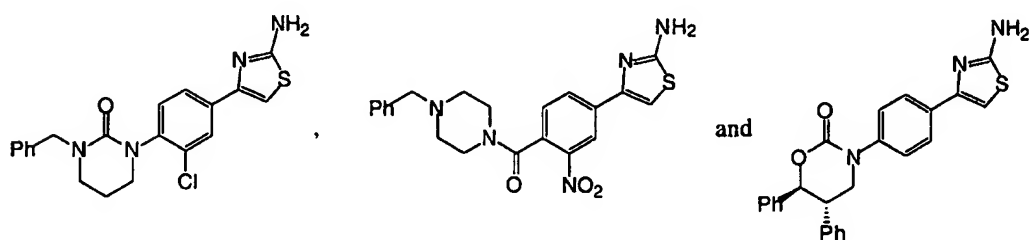
73. A method in accordance with claim 52, said compound selected from the group consisting of:



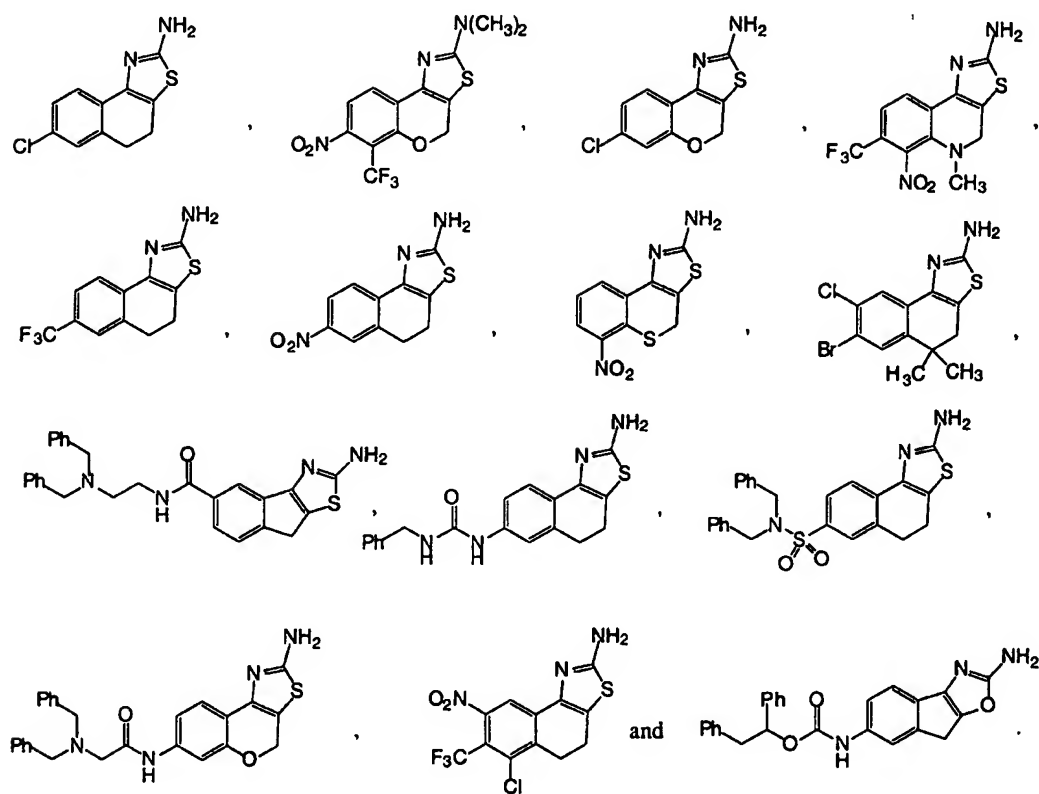
74. A pharmaceutical composition of claim 26, said compound selected from the group consisting of:



75. A method in accordance with claim 52, said compound selected from the group consisting of:



76. A method in accordance with claim 52, said compound selected from the group consisting of:



77. A method in accordance with claim 52, wherein said compound is administered in conjunction with an ancillary antiviral compound selected from the group consisting of ganciclovir, famciclovir, valaciclovir, foscarnet and cidofovir.

78. A method in accordance with claim 52, wherein said compound is administered to a patient having a sexually-transmitted viral disease.

79. A method in accordance with claim 52, wherein said mammal is in an immunocompromised condition.

80. A method in accordance with claim 52, wherein said administering is oral.

81. A method in accordance with claim 52, wherein said administering is topical.

82. A method in accordance with claim 52, wherein said administering is prophylactic to prevent the onset of viral infection, said onset occurring via sexual transmission.

- 83.** A method in accordance with claim 52, wherein said viral infection is a virus selected from the group consisting of HSV1, HSV2, Epstein Barr virus and varicella zoster virus.
- 84.** A method in accordance with claim 52, wherein said administering is parenteral.
- 85.** A method of blocking herpes virus replication by inhibiting the herpes helicase-primase enzyme complex activity, said method comprising contacting said virus with a compound of claim 1 in a herpes helicase-primase enzyme complex inhibiting amount.
- 86.** A method in accordance with claim 85, wherein the herpes virus is selected from the group consisting of HSV-1 and HSV-2.

FIGURE 1A

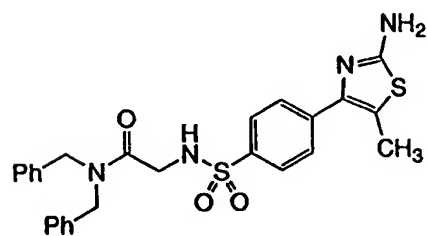
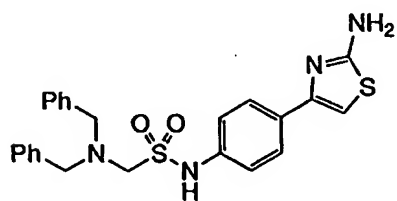
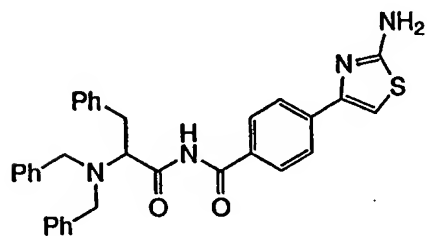
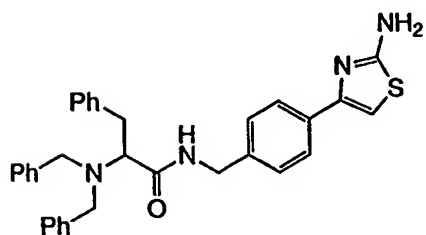
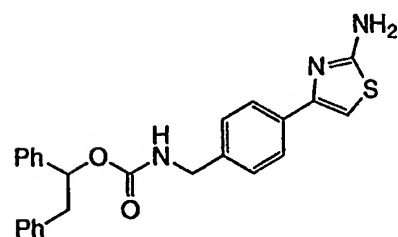
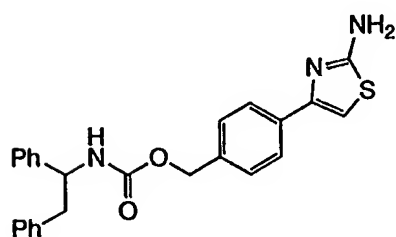
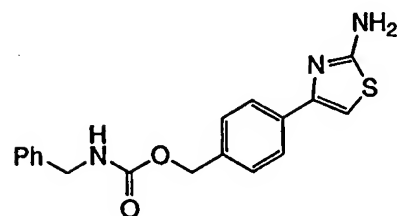
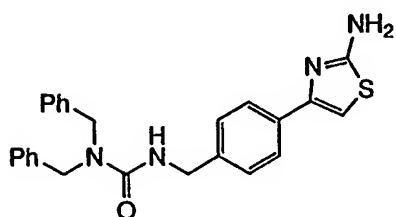
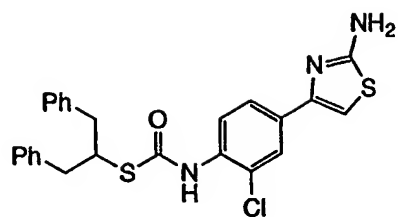
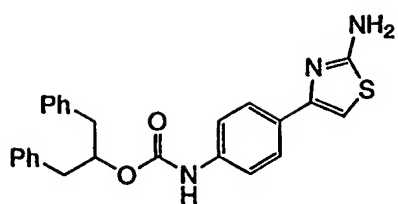


FIGURE 1B

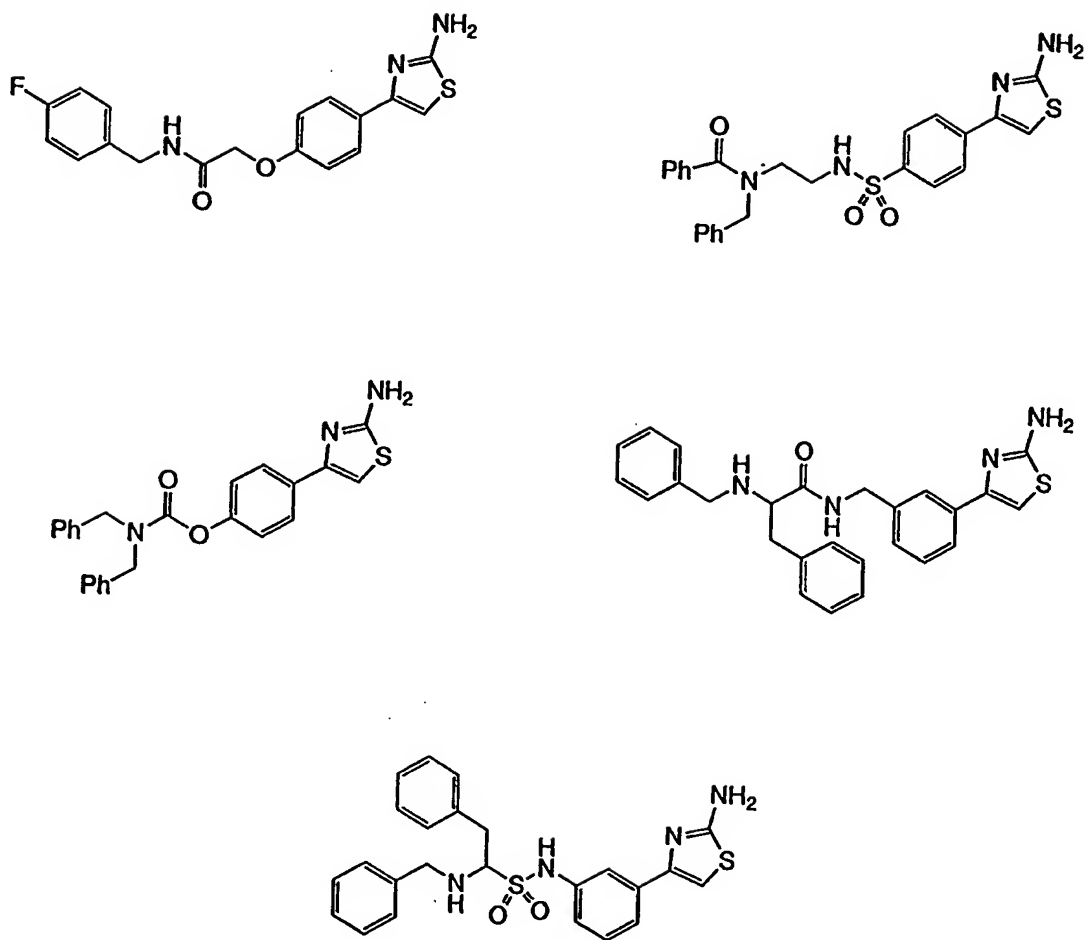


FIGURE 2A

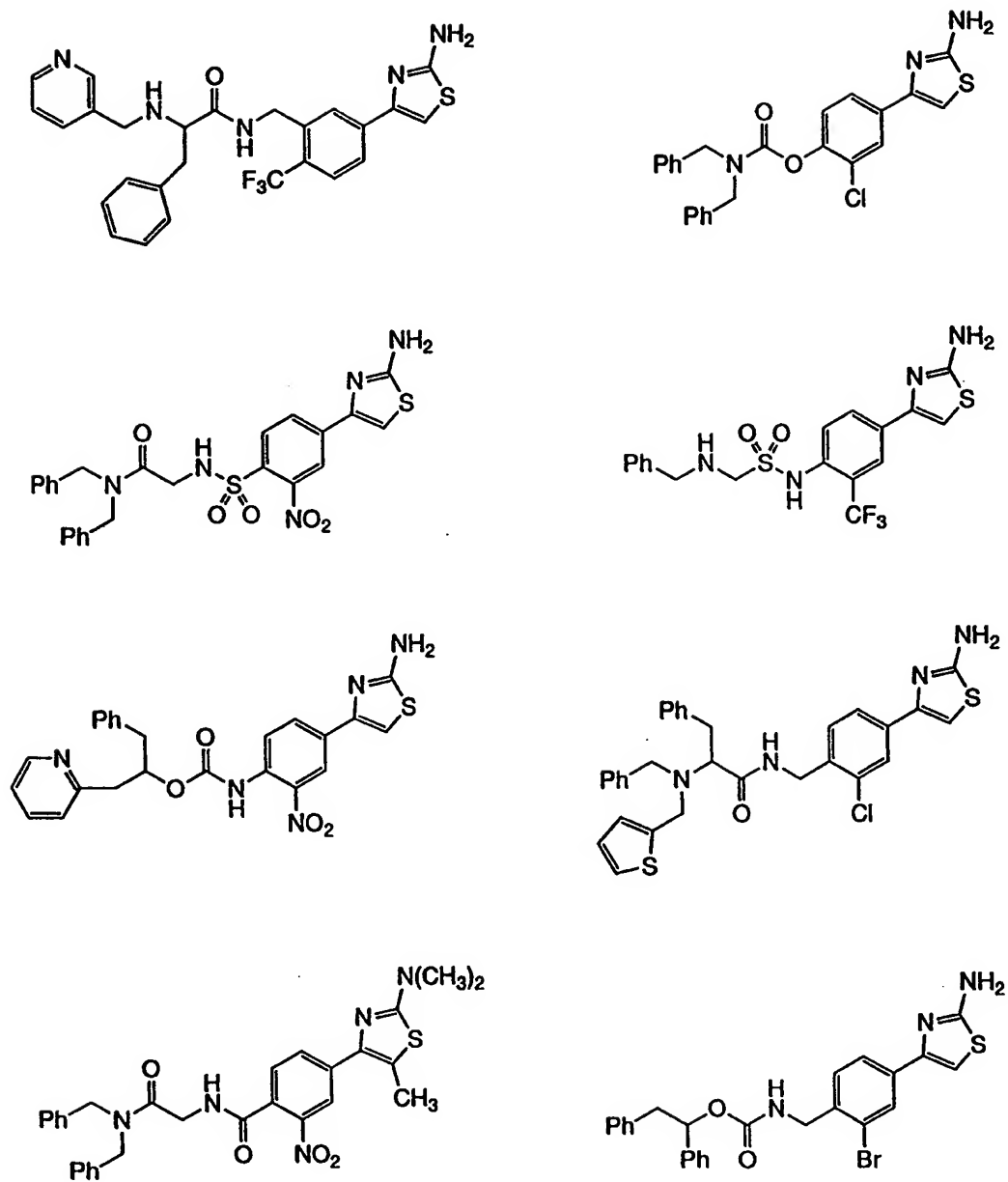


FIGURE 2B

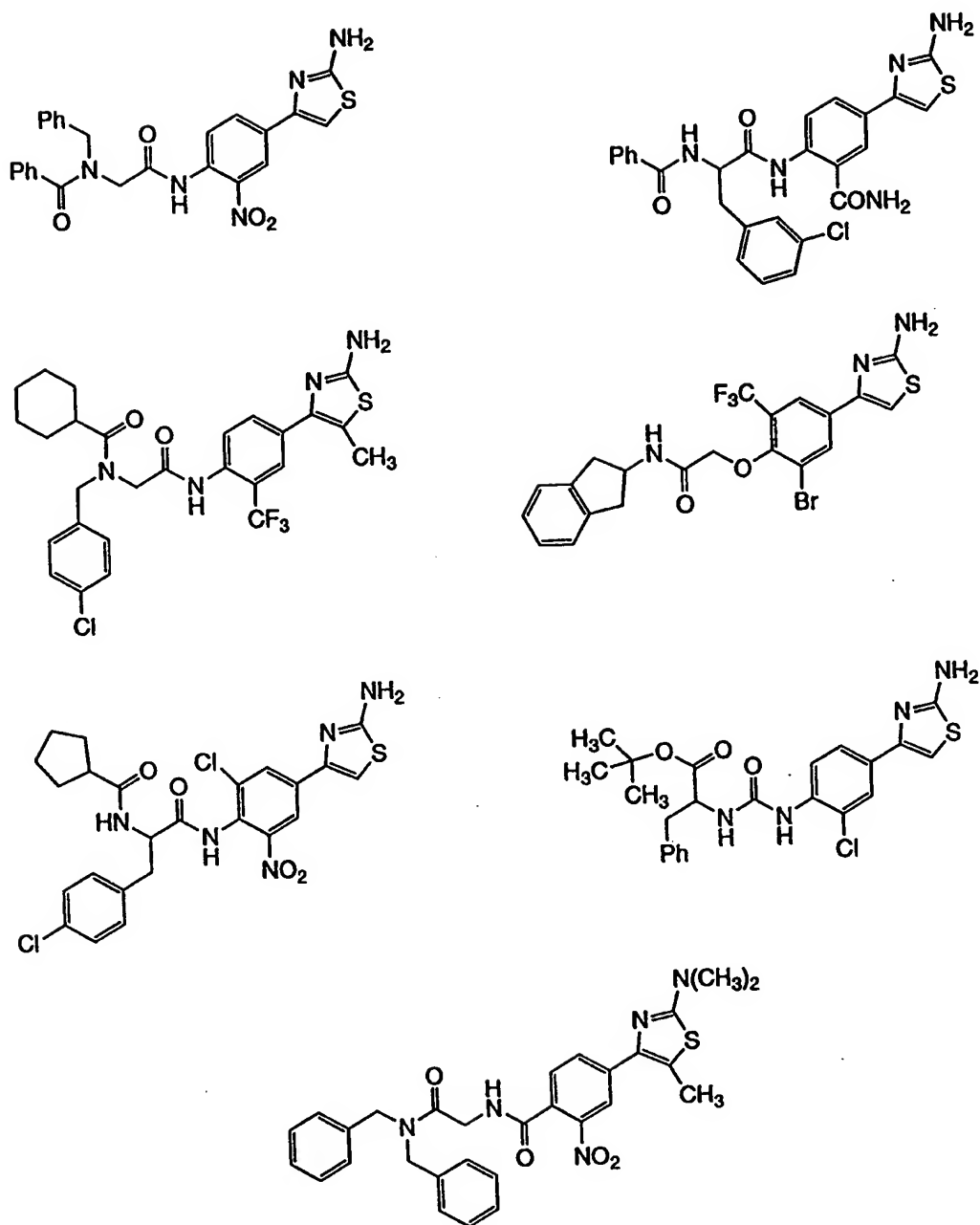


FIGURE 3

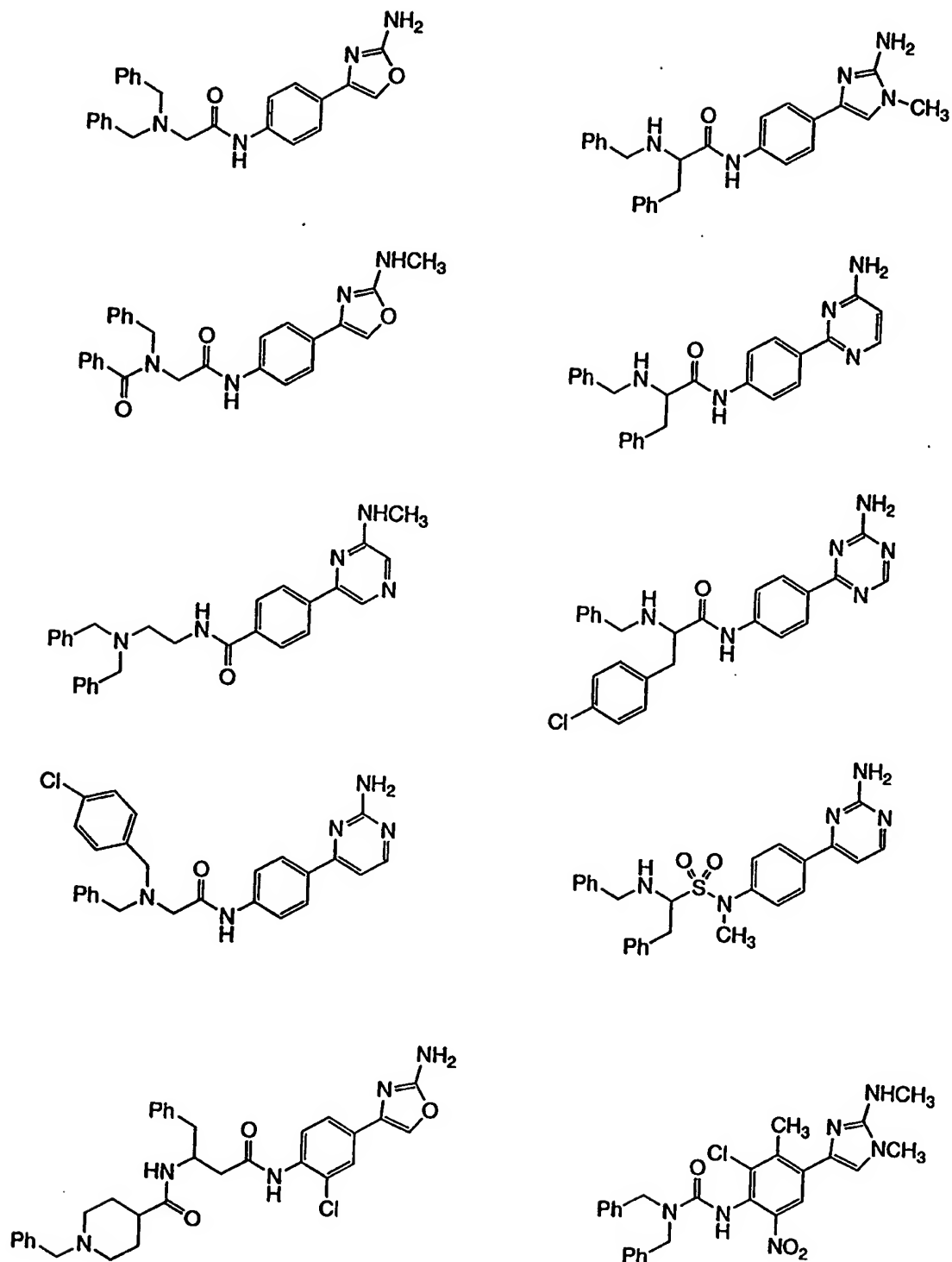


FIGURE 4

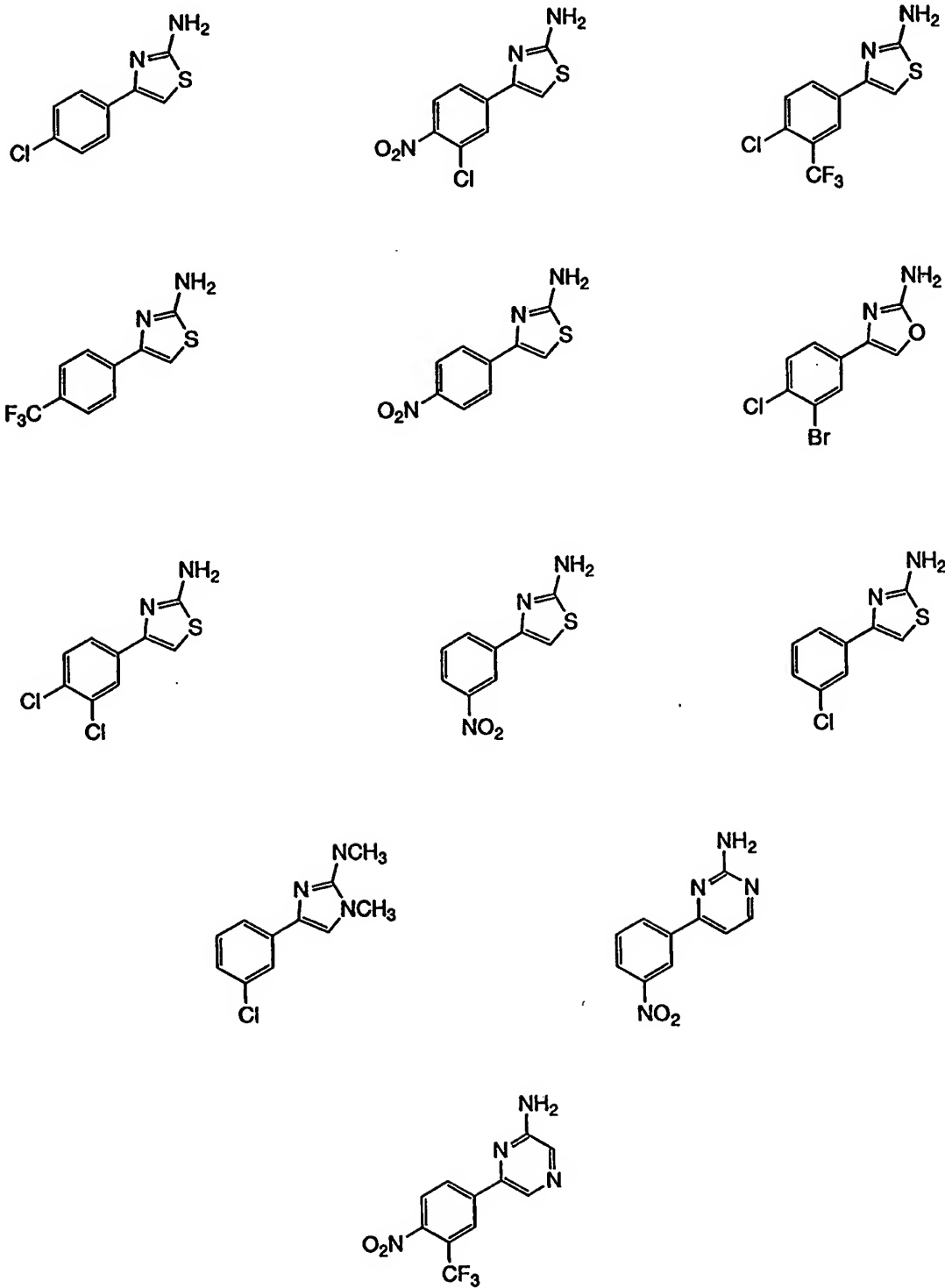


FIGURE 5A

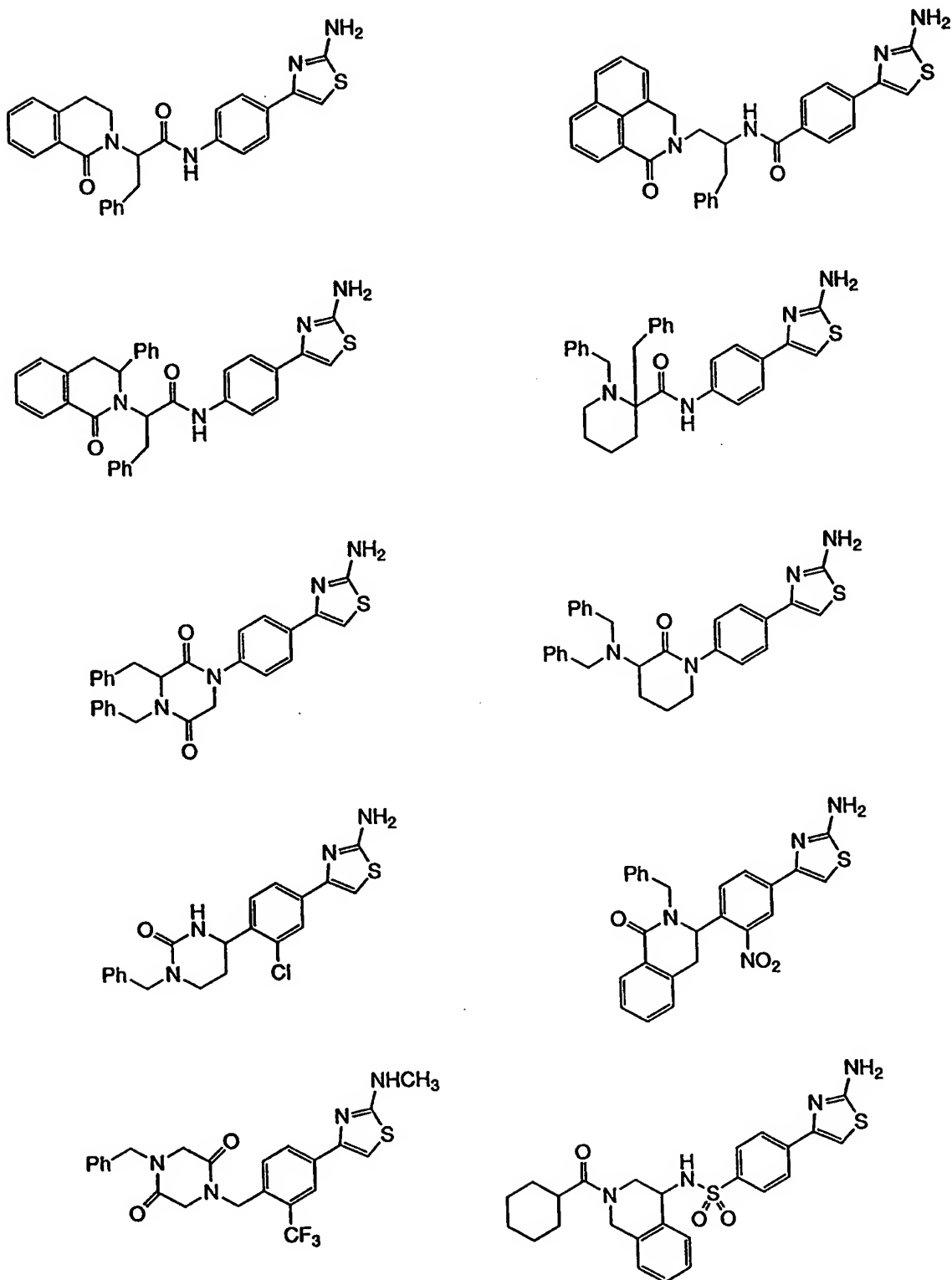


FIGURE 5B

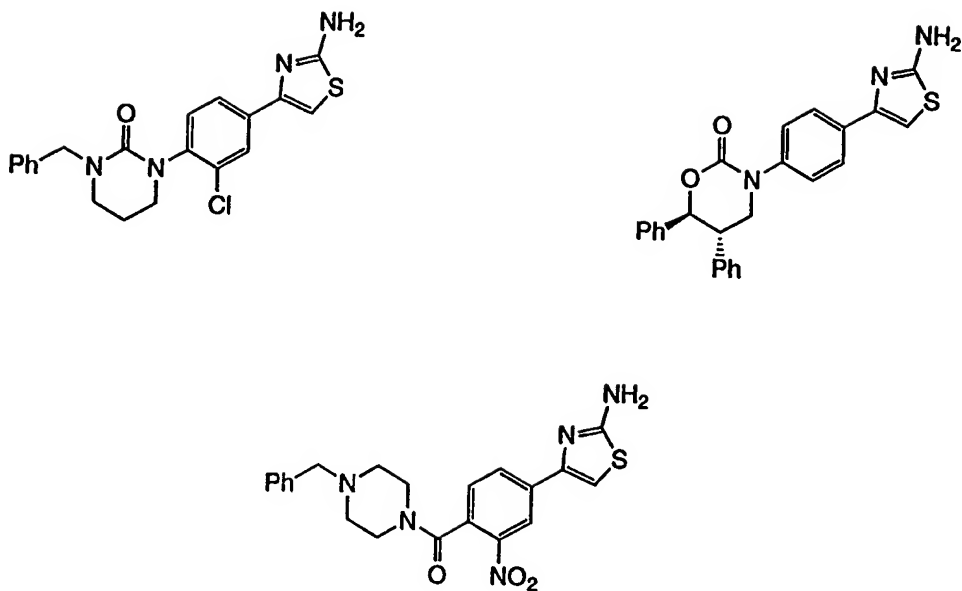
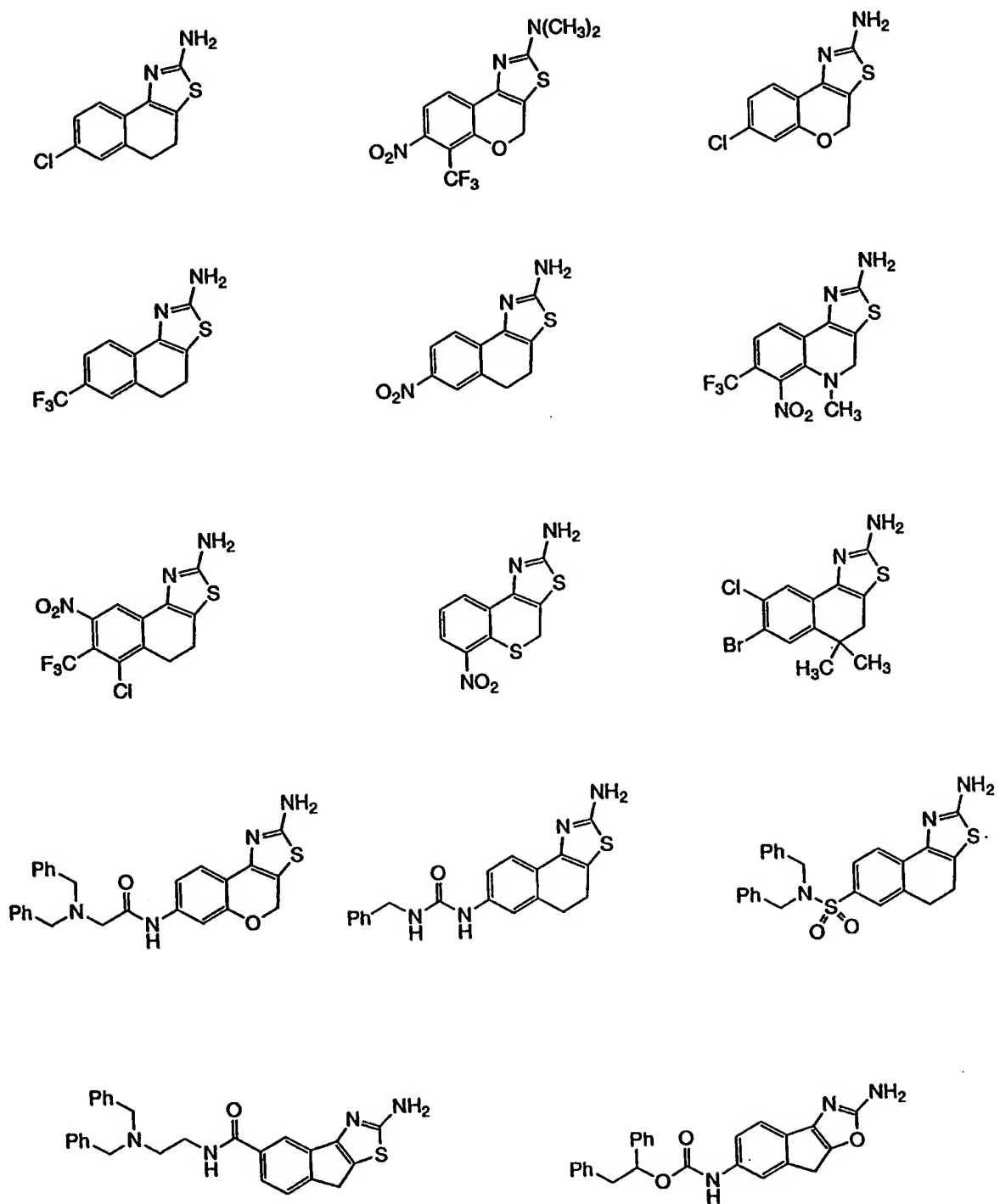


FIGURE 6



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/02947

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 277/40; A61K 31/425

US CL :548/194, 197, 199:514/370

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/194, 197, 199:514/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
cas online**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DICKER, I.B. et al. Herpes Simplex Type 1: lacZ Recombinant Viruses II. Microtiter plate-based colorimetric assays for the discovery of new antiherpes agents and the points at which such agents disrupt the viral replication cycle. Antiviral Research. 1995, Vol. 28, No. 3, pp. 213-224, see Fig. 2.	1 - 1 - 7, 11, 26 - 32, 36, 52 - 58, 62, 77-86



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 APRIL 1999

Date of mailing of the international search report

19 MAY 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ROBERT GERSTL

Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/02947**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-14, 17-20, 22-24, 26-39, 42-45, 47-65, 68-71, 73-75, 77-85

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/02947

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

- 1,3 thiazoles
- 1,3 oxazoles
- 1,3 diazoles
- 1,4 diazines
- 1,3 diazines
- 1,3,5 triazines
- fused thiazoles
- fused oxazoles

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the compounds all exhibit a distinct heterocyclic core.

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